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(54) Title: T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES, AND USES THEREOF

(57) Abstract

The present invention relates to TCR Vβ proteins; to TCR Vβ nucleic acid molecules, including those that encode such TCR Vβ proteins; to antibodies raised against such TCR Vβ proteins; and to therapeutic compounds that regulate TCR Vβ function. The present invention also includes methods to identify and obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to regulate an immune response in an animal. Also included in the present invention are methods to detect T cell expansion in an animal using reagents including, or derived from such proteins, nucleic acid molecules or antibodies.

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"T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES, AND USES THEREOF "

FIELD OF THE INVENTION

The present invention relates to T cell receptor beta chain variable region nucleic acid molecules, proteins encoded by such nucleic acid molecules, antibodies raised against such proteins and inhibitors of such proteins or nucleic acid molecules. The present invention also includes therapeutic compositions comprising such nucleic acid molecules, proteins, antibodies and/or inhibitors, as well as their use to regulate an immune response in an animal.

BACKGROUND OF THE INVENTION

The immune system of an animal is characterized by its ability to respond to a diverse set of antigenic determinants, or epitopes. This response is reflected through T and B lymphocytes, also referred to as T cells and B cells, respectively. The immune system, comprising these specialized cells, recognizes and processes foreign pathogens and macromolecules. Lymphocytes individually exhibit high specificity in recognition of particular molecular structures of antigens. The structural properties are recognized by T cell receptors, which act as antigen receptors.

T cell receptors (TCR) are members of the immunoglobulin superfamily. A TCR molecule comprises two polypeptide chains, generally an alpha chain and a beta chain. Each chain comprises an amino terminal variable region domain (V) and a carboxyl terminal constant region domain (C), and can be designated with α or β when indicating the particular chain of origin. V and C regions are encoded by V region or C region genes, respectively. Each domain can be stabilized by a disulfide bond between two conserved cysteine residue pairs on each chain. Each chain is anchored to the cell membrane by a hydrophobic transmembrane domain, which typically spans the entire lipid bilayer of the membrane. A short carboxyl domain extends into the cytoplasm.

The α and β chains of the TCR are encoded by gene segments analogous to the variable region (V), the diversity region (D), the joining region (J) and the constant region (C) of immunoglobulin genes. Diversity in the TCR repertoire arises, in part,

from the rearrangement of V, D and J regions and from the insertion of or deletion of nucleotides at the junction between the V, D and J regions.

Previous investigators have described TCR beta chain sequences, e.g., Malisson et al., *Cell*, vol. 37, pp. 1101-1110, 1984; Patten et al., *Nature*, vol. 312, pp. 40-46, 1984; Davis et al., *Nature*, vol. 334, pp. 395-402, 1988; Hood et al., U.S. Patent No. 4,886,743, issued Dec. 12, 1989; and Makrides et al., U.S. Patent No. 5,552,300, issued Sep. 3, 1996.

T cells play a pivotal role in the differentiation and regulation of immune cells. Previous investigators have studied diseases in which there appears to be improper immune regulation, such as autoimmunity and some forms of immunodeficiency, and have implicated T cells in the pathogenesis of such diseases. In addition, situations exist in which clonal or oligoclonal expansion of a particular T cell population, identified by the presence of a particular TCR, can be representative of a disease state. One example is the presence of malignancy which has resulted in a T cell leukemia or lymphoma (e.g., Hood et al., *ibid.*). In situations of T cell leukemias or lymphomas, a TCR acts as a unique tumor marker since the TCR is stably rearranged and presented on the surface of the cell.

In summary, there remains a need to develop methods and compounds useful for the detection and treatment of undesired immune responses involving T cells.

SUMMARY OF THE INVENTION

The present invention relates to T cell receptor nucleic acid molecules, proteins encoded by such nucleic acid molecules, antibodies raised against such proteins and inhibitors of such proteins or nucleic acid molecules. The present invention also includes therapeutic compositions comprising such nucleic acid molecules, proteins, antibodies and/or inhibitors, as well as their use to regulate an immune response in an animal. The present invention also includes methods to detect T cell expansion using reagents including or derived from such nucleic acid molecules, proteins and/or antibodies, as well as the use of such methods to diagnose abnormal states or disease in an animal.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 illustrates PCR amplified TCR Vβ DNA using DNA from tissue of normal dogs and dogs having lymphoma.

Figs. 2A, 2B and 2C illustrate fingerprints of TCR Vβ DNA from a normal dog.

Figs. 3A, 3B and 3C illustrate fingerprints of TCR Vβ DNA from a dog having lymphoma.

Fig. 4 illustrates a comparison between fingerprints of TCR Vβ DNA from a normal dog and a dog having lymphoma.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for isolated T cell receptor beta chain variable region (TCR Vβ) proteins, isolated TCR Vβ nucleic acid molecules, antibodies directed against TCR Vβ proteins, and compounds derived therefrom that regulate the immune response of an animal. A TCR Vβ protein can refer to a TCR Vβ protein or a homolog thereof. As used herein, the term "TCR Vβ" refers to a molecule that can include the variable (V) region, alone or in combination with the diversity (D) and/or joining (J) regions of a TCR beta chain. It is known to one of skill in the art that the size and sequence of V, D and J regions of a TCR beta chain can vary as a result of any given recombination event between genes encoding such V, D and J regions. Typical consensus sequences used to identify the junction between the V, D and J regions are also known to one of skill in the art, thereby enabling the identification of the size and sequence of the V, D or J regions of a TCR beta chain from a novel nucleic acid or amino acid sequence. Compounds derived from TCR Vβ proteins or nucleic acid molecules of the present invention include compounds including at least a portion of, or designed using, such proteins or nucleic acid molecules.

As used herein, the phrase "regulate an immune response" refers to modulating the activity of cells involved in an immune response. The term "regulate" can refer to increasing or decreasing an immune response Regulation of an immune response can be determined using methods known in the art as well as methods disclosed herein. As used herein, the terms isolated TCR Vβ proteins and isolated TCR Vβ nucleic acid molecules refers to TCR Vβ proteins and TCR Vβ nucleic acid molecules derived from mammals, preferably canids, more preferably dogs, and, as such, can be obtained from

their natural source, or can be produced using, for example, recombinant nucleic acid technology or chemical synthesis. Also included in the present invention is the use of these proteins, nucleic acid molecules, antibodies, and compounds derived therefrom as therapeutic compositions to regulate the immune response of an animal as well as in other applications, such as those disclosed below.

One embodiment of the present invention is an isolated protein that includes a TCR Vβ protein. It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, a protein refers to one or more proteins or at least one protein. As such, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. According to the present invention, an isolated, or biologically pure, protein, is a protein that has been removed from its natural milieu. As such, "isolated" and "biologically pure" do not necessarily reflect the extent to which the protein has been purified. An isolated protein of the present invention can be obtained from its natural source, can be produced using recombinant DNA technology, or can be produced by chemical synthesis.

As used herein, an isolated TCR Vβ protein of the present invention (i.e., a TCR Vβ protein) can be a full-length protein or any homolog of such a protein. Full-length proteins can refer to proteins having the V, D, J and C regions of a beta chain or one or more of such regions. It is to be noted that the term "a homolog" refers to one or more or at least one homolog. An isolated protein of the present invention, including a homolog, can be identified in a straight-forward manner by the protein's ability to elicit an immune response against a TCR Vβ protein or to bind to a major histocompatability (MHC) molecule or superantigen. Examples of TCR Vβ homologs include TCR Vβ proteins in which amino acids have been deleted (e.g., a truncated version of the protein, such as a peptide), inserted, inverted, substituted and/or derivatized (e.g., by glycosylation, phosphorylation, acetylation, myristoylation, prenylation, palmitoylation, amidation and/or addition of glycerophosphatidyl inositol) such that the homolog includes at least one epitope capable of eliciting an immune response against a TCR Vβ protein, and/or of binding to an antibody directed against a TCR Vβ protein. That is, when the homolog is administered to an animal as an immunogen, using techniques

known to those skilled in the art, the animal will produce an immune response against at least one epitope of a natural TCR Vβ protein. The ability of a protein to effect an immune response can be measured using techniques known to those skilled in the art. As used herein, the term "epitope" refers to the smallest portion of a protein or other antigen capable of selectively binding to the antigen binding site of an antibody. It is well accepted by those skilled in the art that the minimal size of a protein epitope is about six to seven amino acids. Other examples of TCR Vβ protein homologs include those homologs that are capable of binding to MHC, in the presence or absence of peptide, or superantigen. The ability of a protein to bind to MHC or superantigen can be measured using various methods well known to those of skill in the art.

TCR Vβ protein homologs can be the result of natural allelic variation or natural mutation. TCR Vβ protein homologs of the present invention can also be produced using techniques known in the art including, but not limited to, direct modifications to the protein or modifications to the gene encoding the protein using, for example, classic or recombinant DNA techniques to effect random or targeted mutagenesis.

TCR Vβ proteins of the present invention are encoded by TCR Vβ nucleic acid molecules. As used herein, a TCR Vβ nucleic acid molecule includes nucleic acid sequences related to a natural TCR Vβ gene. It is to be noted that the term "a nucleic acid molecule", "a gene" or "a nucleic acid sequence" refers to one or more or at least one nucleic acid molecule, gene or nucleic acid sequence, respectively. As used herein, a TCR Vβ gene includes all regions of the gene such as regulatory regions that control production of the TCR Vβ protein encoded by the gene (such as, but not limited to, transcription, translation or post-translation control regions) as well as the coding region itself, and any introns or non-translated coding regions. As used herein, a gene that "includes" or "comprises" a sequence may include that sequence in one contiguous array, or may include the sequence as fragmented exons. As used herein, the term "coding region" refers to a continuous linear array of nucleotides that translates into a protein. A full-length coding region is that coding region that is translated into a full-length, i.e., a complete, protein as would be initially translated in its natural milieu, prior to any post-translational modifications.

In one embodiment, a TCR Vβ gene of the present invention includes the nucleic acid sequence SEQ ID NO:1, as well as the complement of SEQ ID NO:1. Nucleic acid sequence SEQ ID NO:1 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule $nCaV\beta3_{381}$, the production of which is disclosed in the Examples. Nucleic acid molecule $nCaV\beta3_{381}$ comprises the coding region for the V, D and J regions of TCRVβ3 (also referred to herein as hcVβ3). The complement of SEQ ID NO:1 (represented herein by SEQ ID NO:3) refers to the nucleic acid sequence of the strand complementary to the strand having SEQ ID NO:1, which can easily be determined by those skilled in the art. Likewise, a nucleic acid sequence complement of any nucleic acid sequence of the present invention refers to the nucleic acid sequence of the nucleic acid strand that is complementary to (i.e., can form a double helix with) the strand for which the sequence is cited. It should be noted that since nucleic acid sequencing technology is not entirely error-free, SEQ ID NO:1 (as well as other nucleic acid and protein sequences presented herein) represents an apparent nucleic acid sequence of the nucleic acid molecule encoding a TCR Vβ protein of the present invention.

In another embodiment, a TCR Vβ gene of the present invention includes the nucleic acid sequence SEQ ID NO:4, as well as the complement of SEQ ID NO:4 represented by SEQ ID NO:6. Nucleic acid sequence SEQ ID NO:4 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule $nCaV\beta4_{408}$, the production of which is disclosed in the Examples. Nucleic acid molecule $nCaV\beta4_{408}$ comprises the coding region for the V, D and J regions of TCRVβ4 (also referred to herein as hcVβ4).

In another embodiment, a TCR Vβ gene of the present invention includes the nucleic acid sequence SEQ ID NO:9, as well as the complement of SEQ ID NO:9 represented by SEQ ID NO:11. Nucleic acid sequence SEQ ID NO:9 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule $nCaV\beta12_{408}$, the production of which is disclosed in the Examples. Nucleic acid molecule $nCaV\beta12_{408}$ comprises the coding region for the V, D and J regions of TCRVβ12 (also referred to herein as hcVβ12).

In another embodiment, a TCR Vβ gene of the present invention includes the nucleic acid sequence SEQ ID NO:98, as well as the complement of SEQ ID NO:98 represented by SEQ ID NO:100. Nucleic acid sequence SEQ ID NO:98 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule $nCaV\beta72_{438}$, the production of which is disclosed in the Examples. Nucleic acid molecule $nCaV\beta72_{438}$ comprises the coding region for the V, D and J regions of TCRVβ72 (also referred to herein as hcVβ72).

In another embodiment, a TCR Vβ gene of the present invention includes the nucleic acid sequence SEQ ID NO:19, as well as the complement of SEQ ID NO:19 represented by SEQ ID NO:19. Nucleic acid sequence SEQ ID NO:19 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule $nCaV\beta21_{462}$, the production of which is disclosed in the Examples. Nucleic acid molecule $nCaV\beta21_{462}$ comprises the coding region for the V, D and J regions of TCRVβ21 (also referred to herein as hcVβ21).

In another embodiment, a TCR Vβ gene of the present invention includes the nucleic acid sequence SEQ ID NO:22, as well as the complement of SEQ ID NO:22 represented by SEQ ID NO:22. Nucleic acid sequence SEQ ID NO:22 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule $nCaV\beta54_{417}$, the production of which is disclosed in the Examples. Nucleic acid molecule $nCaV\beta54_{417}$ comprises the coding region for the V, D and J regions of TCRVβ54 (also referred to herein as dtb54).

In another embodiment, a TCR Vβ gene of the present invention includes the nucleic acid sequence SEQ ID NO:25, as well as the complement of SEQ ID NO:25 represented by SEQ ID NO:25. Nucleic acid sequence SEQ ID NO:25 represents the deduced sequence of the coding strand of a cDNA (complementary DNA) denoted herein as nucleic acid molecule $nCaV\beta182_{423}$, the production of which is disclosed in the Examples. Nucleic acid molecule $nCaV\beta182_{423}$ comprises the coding region for the V, D and J regions of TCRVβ182 (also referred to herein as dtb182).

In another embodiment, a TCR Vβ gene or nucleic acid molecule can be an allelic variant that includes a similar but not identical sequence to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:11, SEQ ID

NO:98, SEQ ID NO:100, or any other TCR Vβ nucleic acid sequence cited herein. An allelic variant of a TCR Vβ nucleic acid molecule including SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:98 and SEQ ID NO:100, is a nucleic acid molecule that occurs at essentially the same locus (or loci) in the genome as the nucleic acid molecule including SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:98 and SEQ ID NO:100, but which, due to natural variations caused by, for example, mutation or recombination, has a similar but not identical sequence. Because natural selection typically selects against alterations that affect function, allelic variants usually encode proteins having similar activity to that of the protein encoded by the gene to which they are being compared. Allelic variants of genes or nucleic acid molecules can also comprise alterations in the 5' or 3' untranslated regions of the gene (e.g., in regulatory control regions), or can involve alternative splicing of a nascent transcript, thereby bringing alternative exons into juxtaposition. Allelic variants are well known to those skilled in the art and would be expected to be found within a given genome, since the respective genomes are diploid, and sexual reproduction will result in the reassortment of alleles.

In one embodiment of the present invention, an isolated TCR Vβ protein is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a gene encoding a TCR Vβ protein (i.e., to a TCR Vβ gene). The minimal size of a TCR Vβ protein of the present invention is a size sufficient to be encoded by a nucleic acid molecule capable of forming a stable hybrid (i.e., hybridize under stringent hybridization conditions) with the complementary sequence of a nucleic acid molecule encoding the corresponding natural protein. The size of a nucleic acid molecule encoding such a protein is dependent on the nucleic acid composition and the percent homology between the TCR Vβ nucleic acid molecule and the complementary nucleic acid sequence. It can easily be understood that the extent of homology required to form a stable hybrid under stringent conditions can vary depending on whether the homologous sequences are interspersed throughout a given nucleic acid molecule or are clustered (i.e., localized) in distinct regions on a given nucleic acid molecule.

Stringent hybridization conditions are determined based on defined physical properties of the gene to which the nucleic acid molecule is being hybridized, and can be defined mathematically. Stringent hybridization conditions are those experimental parameters that allow an individual skilled in the art to identify significant similarities between heterologous nucleic acid molecules. These conditions are well known to those skilled in the art. See, for example, Sambrook, *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, and Meinkoth, *et al.*, 1984, *Anal. Biochem. 138*, 267-284. As explained in detail in the cited references, the determination of hybridization conditions involves the manipulation of a set of variables including the ionic strength (expressed as molarity (M), in moles/liter), the hybridization temperature (°C), the concentration of nucleic acid helix destabilizing agents (such as formamide), the average length of the shortest hybrid duplex (n), and the percent G + C composition of the fragment to which an unknown nucleic acid molecule is being hybridized. For nucleic acid molecules longer than about 50 nucleotides, these variables are inserted into a standard mathematical formula to calculate the melting temperature, or T_m, of a given nucleic acid molecule. As defined in the formula below, T_m is the temperature at which two complementary nucleic acid molecule strands will disassociate, assuming 100% complementarity between the two strands:

$$T_m = 81.5°C + 16.6 \log M + 0.41(\% G + C) - 500/n - 0.61(\% \text{ formamide}).$$

For nucleic acid molecules smaller than about 50 nucleotides, hybrid stability is defined by the dissociation temperature (T_d), which is defined as the temperature at which 50% of the duplexes dissociate. For these smaller molecules, the stability at a standard ionic strength is defined by the following equation:

$$T_d = 4(G + C) + 2(A + T).$$

A temperature of 5°C below T_d is used to detect hybridization between perfectly matched molecules.

Also well known to those skilled in the art is how base-pair mismatch, i.e. differences between two nucleic acid molecules being compared, including non-complementarity of bases at a given location, and gaps due to insertion or deletion of one or more bases at a given location on either of the nucleic acid molecules being compared, will affect T_m or T_d for nucleic acid molecules of different sizes. For

example, T_m decreases about 1°C for each 1% of mismatched base-pairs for hybrids greater than about 150 bp, and T_d decreases about 5°C for each mismatched base-pair for hybrids below about 50 bp. Conditions for hybrids between about 50 and about 150 base-pairs can be determined empirically and without undue experimentation using standard laboratory procedures well known to those skilled in the art. These simple procedures allow one skilled in the art to set the hybridization conditions (by altering, for example, the salt concentration, the formamide concentration or the temperature) so that only nucleic acid hybrids with greater than a specified % base-pair mismatch will hybridize. Stringent hybridization conditions are commonly understood by those skilled in the art to be those experimental conditions that will allow about 30% base-pair mismatch (i.e., about 70% identity). Because one skilled in the art can easily determine whether a given nucleic acid molecule to be tested is less than or greater than about 50 nucleotides, and can therefore choose the appropriate formula for determining hybridization conditions, he or she can determine whether the nucleic acid molecule will hybridize with a given nucleic acid molecule under stringent hybridization conditions and similarly whether the nucleic acid molecule will hybridize under conditions designed to allow a desired amount of base pair mismatch.

Hybridization reactions are often carried out by attaching the nucleic acid molecule to be hybridized to a solid support such as a membrane, and then hybridizing with a labeled probe suspended in a hybridization solution. Examples of common hybridization reaction techniques include the well-known Southern and northern blotting procedures. Typically, the actual hybridization reaction is done under non-stringent conditions, i.e., at a lower temperature and/or a higher salt concentration, and then high stringency is achieved by washing the membrane in a solution with a higher temperature and/or lower salt concentration in order to achieve the desired stringency.

For example, if the skilled artisan wished to identify a nucleic acid molecule that hybridizes under stringent hybridization conditions with a specific or known canine nucleic acid molecule of about 150 bp in length, the following conditions could preferably be used. The average G + C content of canine DNA includes about 35%, about 36%, about 37%, about 38%, about 39%, about 41%, about 42%, about 43%, about 44%, about 45%, with about 40% being preferred. The unknown nucleic acid

molecules would be attached to a support membrane, and the specified 150 bp nucleic acid molecule would be labeled, e.g. with a radioactive tag. The hybridization reaction could be carried out in a solution comprising 2X SSC and 0% formamide, at a temperature of about 37°C (low stringency conditions). Solutions of differing concentrations of SSC can be made by one of skill in the art by diluting a stock solution of 20X SSC (175.3 gram NaCl and about 88.2 gram sodium citrate in 1 liter of water, pH 7) to obtain the desired concentration of SSC. In order to achieve high stringency hybridization, the skilled artisan would calculate the washing conditions required to allow up to 30% base-pair mismatch. For example, in a wash solution comprising 1X SSC and 0% formamide, the T_m of perfect hybrids would be about 80.8°C:

$$81.5°C + 16.6 \log (.15M) + (0.41 \times 40) - (500/150) - (0.61 \times 0) = 80.8°C.$$

Thus, to achieve hybridization with nucleic acid molecules having about 30% base-pair mismatch, hybridization washes would be carried out at a temperature of about 50.8°C. It is within the skill of one in the art to calculate the hybridization temperature based on the formulae and G/C content disclosed herein.

In one embodiment of the present invention, a preferred TCR Vβ nucleic acid molecule includes a nucleic acid molecule which has greater than about 50 base pairs and which hybridizes under conditions which preferably allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Another preferred TCR Vβ nucleic acid molecule of the present invention includes a nucleic acid molecule which has greater than about 150 base pairs and which hybridizes under conditions which preferably allow about 30% base pair mismatch,

more preferably under conditions which allow about 25% base pair mismatch, more preferably under conditions which allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Another preferred TCR Vβ nucleic acid molecule of the present invention includes a nucleic acid molecule which has greater than about 200 base pairs and which hybridizes under conditions which preferably allow about 30% base pair mismatch, more preferably under conditions which allow about 25% base pair mismatch, more preferably under conditions which allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73 or SEQ ID NO:74.

Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 49°C, to an isolated

nucleic acid molecule selected from the group consisting of SEQ ID NO:3, SEQ ID NO:30, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61 or SEQ ID NO:62.

Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 56°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:5, SEQ ID NO:8, SEQ ID NO:33, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:63, SEQ ID NO:64 or SEQ ID NO:65. Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 53°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:36, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:66, SEQ ID NO:67 or SEQ ID NO:68. Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 41°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:39, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71. Another embodiment of the present invention includes a nucleic acid molecule comprising at least about 150 base-pairs, wherein said molecule hybridizes, in a solution comprising 1X SSC and 0% formamide, at a temperature of about 29°C, to an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:42, the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:72, SEQ ID NO:73 or SEQ ID NO:74.

Another embodiment of the present invention includes TCR Vβ proteins. A preferred TCR Vβ protein includes a protein encoded by a nucleic acid molecule which has greater than about 50 base pairs and which hybridizes under conditions which

preferably allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80.

Another preferred TCR Vβ protein of the present invention includes a protein encoded by a nucleic acid molecule which has greater than about 150 base pairs and which hybridizes under conditions which preferably allow about 30% base pair mismatch, more preferably under conditions which allow about 25% base pair mismatch, more preferably under conditions which allow about 20% base pair mismatch, more preferably under conditions which allow about 15% base pair mismatch, more preferably under conditions which allow about 10% base pair mismatch and even more preferably under conditions which allow about 5% base pair mismatch with a nucleic acid molecule selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80.

Another preferred TCR Vβ protein of the present invention includes a protein encoded by a nucleic acid molecule which has greater than about 50 base pairs which is preferably about 80% identical, more preferably about 85% identical, more preferably

about 90% identical, and even more preferably about 95% identical to a nucleic acid molecule having the nucleic acid sequence SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Yet another preferred TCR Vβ of the present invention includes a protein encoded by a nucleic acid molecule which has greater than about 150 base pairs which is preferably about 70% identical, more preferably about 75% identical, more preferably about 80% identical, more preferably about 85% identical, more preferably about 90% identical and even more preferably about 95% identical to a nucleic acid molecule having the nucleic acid sequence SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 or SEQ ID NO:71.

Yet another preferred TCR Vβ of the present invention includes a protein encoded by a nucleic acid molecule which has greater than about 200 base pairs which is preferably about 70% identical, more preferably about 75% identical, more preferably about 80% identical, more preferably about 85% identical, more preferably about 90% identical and even more preferably about 95% identical to a nucleic acid molecule having the nucleic acid sequence SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ

ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73 or SEQ ID NO:74.

The minimal size of such a nucleic acid molecule is typically at least about 12 to about 15 nucleotides in length if the nucleic acid molecule is GC-rich and at least about 15 to about 17 bases in length if the nucleic acid molecule is AT-rich. The minimal size of a nucleic acid molecule used to encode a TCR Vβ protein homolog of the present invention is from about 12 to about 18 nucleotides in length. Thus, the minimal size of a TCR Vβ protein homolog of the present invention is from about 4 to about 6 amino acids in length. There is no limit, other than a practical limit, on the maximal size of a nucleic acid molecule encoding a TCR Vβ protein or protein homolog because a nucleic acid molecule of the present invention can include a portion of a gene, an entire gene, or multiple genes. The preferred size of a protein encoded by a nucleic acid molecule of the present invention depends on whether a full-length, fusion, multivalent, or functional portion of such a protein is desired. As used herein, "fragments thereof" and "portions thereof" are intended to be used interchangeably, and have a minimal size as disclosed herein.

The minimal size of a protein or nucleic acid molecule of the present invention also can include a portion of a protein or nucleic acid molecule that is less than 100% identical to another protein or nucleic acid molecule, when determined using hybridization or computer alignment methods disclosed herein. For example, a fragment of a hcVβ3 protein of the present invention is at least about 15 residues, preferably 20 residues and more preferably 25 residues in length; a fragment of a hcVβ4 protein of the present invention is at least about 10 residues, preferably 15 residues and more preferably 20 residues in length; a fragment of a hcVβ12 protein of the present invention is at least about 11 residues, preferably 15 residues and more preferably 20 residues in length; a fragment of a hcVβ72 protein of the present invention is at least about 18 residues, preferably 25 residues and more preferably 30 residues in length; or a fragment of a hcVβ21 protein of the present invention is at least about 13 residues, preferably 20 residues and more preferably 25 residues in length. In addition, a nucleic acid molecule fragment of a hcVβ3 nucleic acid molecule of the present invention is at least about 33 nucleotides, preferably 35 nucleotides and more preferably 40 nucleotides in length; a

fragment of a hcVβ4 nucleic acid molecule of the present invention is at least about 21 nucleotides, preferably 25 nucleotides and more preferably 30 nucleotides in length; a fragment of a hcVβ12 nucleic acid molecule of the present invention is at least about 19 nucleotides, preferably 25 nucleotides and more preferably 30 nucleotides in length; a fragment of a hcVβ72 nucleic acid molecule of the present invention is at least about 27 nucleotides, preferably 30 nucleotides and more preferably 35 nucleotides in length; or a fragment of a hcVβ21 nucleic acid molecule of the present invention is at least about 176 nucleotides, preferably 180 nucleotides and more preferably 185 nucleotides in length.

Suitable protein fragments of the present invention include functional portions of a TCR Vβ protein of the present invention including, but not limited to, epitopes, MHC and/or peptide recognition sequences, antigen recognition sequences, superantigen recognition sequences, framework V regions and hypervariable V regions. Preferred functional portions of a TCR Vβ protein include the V, D or J regions. More preferred functional portions of a TCR Vβ protein include: the putative signal peptide encoded by about nucleotide 1 to nucleotide 51, the V region encoded by about nucleotide 52 to about nucleotide 333, and the D/J region encoded by about nucleotide 334 to about nucleotide 381 of SEQ ID NO:1; the putative signal peptide encoded by nucleotide 25 to nucleotide 69, the V region encoded by nucleotide 70 to about nucleotide 351, and the D/J region encoded by about nucleotide 352 to about nucleotide 408 of SEQ ID NO:4; the putative signal peptide encoded by nucleotide 7 to nucleotide 63, the V region encoded by nucleotide 64 to about nucleotide 339, and the D/J region encoded by about nucleotide 340 to about nucleotide 408 of SEQ ID NO:9; the putative signal peptide encoded by nucleotide 85 to nucleotide 141, the V region encoded by nucleotide 142 to about nucleotide 423, and the D/J region encoded by about nucleotide 424 to about nucleotide 438 of SEQ ID NO:98; the putative signal peptide encoded by nucleotide 73 to nucleotide 114, the V region encoded by nucleotide 115 to about nucleotide 396, and the D/J region encoded by about nucleotide 397 to about nucleotide 462 of SEQ ID NO:19; the putative signal peptide encoded by nucleotide 13 to nucleotide 69, the V region encoded by nucleotide 70 to about nucleotide 354, and the D/J region encoded by about nucleotide 355 to about nucleotide 417 of SEQ ID NO:22; and the putative signal

peptide encoded by nucleotide 40 to nucleotide 96, the V region encoded by nucleotide 97 to about nucleotide 369, and the D/J region encoded by about nucleotide 370 to about nucleotide 423 of SEQ ID NO:25.

It is known to those of skill in the art that the junction between the V and D region can vary but that typically the carboxyl end of the V region contains one or more of the amino acid residues alanine or serine following a cysteine. For example, one of skill in the art would know that a conserved carboxyl V region sequence comprises the amino acids CASS. Thus, a V region of the present invention can include the amino acid sequence SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80. The present invention includes nucleic acid molecules having nucleic acid sequences encoding such proteins, which can be identified using the nucleic acid sequences disclosed herein and standard codon usage known to those of skill in the art; such as disclosed, for example, in Lehninger, *Biochemistry*, Worth Publishers, Inc., 1975, which is incorporated herein by this reference in its entirety. For example, a skilled artisan would know that codons encoding serine include ACA, ACC, AGT, AGC or ACG, and codons that encode alanine include GCA, GCC, GCT or GCG.

One embodiment of a TCR Vβ protein of the present invention is a fusion protein that includes a TCR Vβ protein-containing domain attached to one or more fusion segments. It is to be noted that the term "a fusion protein" refers to one or more or at least one fusion protein. Suitable fusion segments for use with the present invention include, but are not limited to, segments that can: enhance a protein's stability; deliver a TCR Vβ protein or portion thereof to a desired target; act as an immunopotentiator to enhance an immune response against a TCR Vβ protein; and/or assist in purification of a TCR Vβ protein (e.g., by affinity chromatography). A suitable fusion segment can be a domain of any size that has the desired function (e.g., imparts increased stability, imparts increased immunogenicity to a protein, and/or simplifies purification of a protein). Fusion segments can be joined to amino and/or carboxyl termini of the TCR Vβ-containing domain of the protein and can be susceptible to

cleavage in order to enable straight-forward recovery of a TCR Vβ protein. Fusion proteins are preferably produced by culturing a recombinant cell transformed with a fusion nucleic acid molecule that encodes a protein including the fusion segment attached to either the carboxyl and/or amino terminal end of a TCR Vβ -containing domain. Preferred fusion segments include a metal binding domain (e.g., a poly-histidine segment); an immunoglobulin binding domain (e.g., Protein A; Protein G; T cell; B cell; Fc receptor or complement protein antibody-binding domains); a sugar binding domain (e.g., a maltose binding domain); and/or a "tag" domain (e.g., at least a portion of -galactosidase, a strep tag peptide, a T7 tag peptide, a Flag™ peptide, or other domains that can be purified using compounds that bind to the domain, such as monoclonal antibodies). More preferred fusion segments include metal binding domains, such as a poly-histidine segment; a maltose binding domain; a strep tag peptide, such as that available from Biometra in Tampa, FL; and an S10 peptide. A preferred fusion protein of the present invention includes a TCR Vβ protein of the present invention linked to a TCR alpha chain in such a manner that the beta chain and alpha chain fold correctly to form a functional dimer. Another preferred fusion protein includes a TCR Vβ protein of the present invention linked to at least a portion of the constant region of an immunoglobulin in such a manner that crystallization of the V beta protein is enhanced by the presence of the immunoglobulin sequence.

Preferably a TCR Vβ protein of the present invention is isolated (including isolation of the natural protein or production of the protein by recombinant or synthetic techniques) from canids.

A preferred isolated protein of the present invention is an isolated protein that is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions with a gene comprising a nucleic acid sequence including SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:24, SEQ ID NO:27, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:45, SEQ ID NO:48, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including

SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80.

A preferred isolated protein of the present invention is a protein encoded by at least one of the following nucleic acid molecules:$nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$,$nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ and/or $nCaV\beta182_{327}$; fragments thereof; or allelic variants of any of these nucleic acid molecules. Another preferred isolated protein is encoded by a nucleic acid molecule having nucleic acid sequence SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:37, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80; fragments thereof or an allelic variant of such a nucleic acid molecule.

Translation of SEQ ID NO:1, the coding strand of $nCaV\beta3_{381}$, yields a TCR Vβ protein of about 127 amino acids containing the beta chain V, D, and J regions, denoted herein as $PCaV\beta3_{127}$, the amino acid sequence of which is presented in SEQ ID NO:2, assuming an open reading frame having a first codon spanning from nucleotide 1 through nucleotide 3 of SEQ ID NO:1 and a last codon spanning from nucleotide 379 through nucleotide 381 of SEQ ID NO:1. The partial putative signal sequence extends from nucleotide 1 to nucleotide 51 of SEQ ID NO:1. The proposed mature protein (i.e.,

canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta3_{110}$, contains about 110 amino acids, extending from residue 18 through residue 127 of SEQ ID NO:2. The nucleic acid molecule encoding $PCaV\beta3_{110}$ is denoted herein as $nCaV\beta3_{330}$, extending from nucleotide 52 through nucleotide 381 of SEQ ID NO:1.

Translation of SEQ ID NO:4, the coding strand of $nCaV\beta4_{408}$, yields a protein of about 128 amino acids containing the beta chain V, D, and J regions, denoted herein as $PCaV\beta4_{128}$, the amino acid sequence of which is presented in SEQ ID NO:5, assuming an open reading frame having an initiation codon spanning from nucleotide 25 through nucleotide 27 of SEQ ID NO:4 and a last codon spanning from nucleotide 406 through nucleotide 408 of SEQ ID NO:4. The coding region encoding $PCaV\beta4_{128}$ is presented herein as $nCaV\beta4_{384}$, which has the nucleotide sequence SEQ ID NO:7 (the coding strand) and SEQ ID NO:8 (the complementary strand). The putative signal sequence extends from nucleotide 25 to nucleotide 69 of SEQ ID NO:4. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta4_{113}$, contains about 113 amino acids, extending from residue 60 through residue 128 of SEQ ID NO:5. The nucleic acid molecule encoding $PCaV\beta4_{113}$ is denoted herein as $nCaV\beta4_{339}$, extending from nucleotide 70 through nucleotide 408 of SEQ ID NO:4.

Translation of SEQ ID NO:9, the coding strand of $nCaV\beta12_{408}$, yields a protein of about 134 amino acids containing the beta chain V, D, and J regions, denoted herein as $PCaV\beta12_{134}$, the amino acid sequence of which is presented in SEQ ID NO:10, assuming an open reading frame having an initiation codon spanning from nucleotide 7 through nucleotide 9 of SEQ ID NO:9 and a last codon spanning from nucleotide 406 through nucleotide 408 of SEQ ID NO:9. The coding region encoding $PCaV\beta12_{134}$ is presented herein as $nCaV\beta12_{402}$, which has the nucleotide sequence SEQ ID NO:12 (the coding strand) and SEQ ID NO:13 (the complementary strand). The putative signal sequence extends from nucleotide 7 to nucleotide 63 of SEQ ID NO:9. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta12_{115}$, contains about 115 amino acids, extending from residue 20 through residue 134 of SEQ ID NO:10. The nucleic acid molecule

encoding PCaVβ12$_{115}$ is denoted herein as nCaVβ12$_{345}$, extending from nucleotide 64 through nucleotide 408 of SEQ ID NO:9.

Translation of SEQ ID NO:98, the coding strand of nCaVβ72$_{438}$, yields a protein of about 133 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaVβ72$_{133}$, the amino acid sequence of which is presented in SEQ ID NO:15, assuming an open reading frame having an initiation codon spanning from nucleotide 85 through nucleotide 87 of SEQ ID NO:98 and a last codon spanning from nucleotide 481 through nucleotide 438 of SEQ ID NO:98. The coding region encoding PCaVβ72$_{133}$ is presented herein as nCaVβ72$_{399}$, which has the nucleotide sequence SEQ ID NO:17 (the coding strand) and SEQ ID NO:18 (the complementary strand). The putative signal sequence extends from nucleotide 85 to nucleotide 141 of SEQ ID NO:98. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as PCaVβ72$_{114}$, contains about 114 amino acids, extending from residue 20 through residue 133 of SEQ ID NO:98. The nucleic acid molecule encoding PCaVβ72$_{114}$ is denoted herein as nCaVβ72$_{342}$, extending from nucleotide 142 through nucleotide 438 of SEQ ID NO:19.

Translation of SEQ ID NO:19, the coding strand of nCaVβ21$_{462}$, yields a protein of about 130 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaVβ21$_{130}$, the amino acid sequence of which is presented in SEQ ID NO:20, assuming an open reading frame having an initiation codon spanning from nucleotide 73 through nucleotide 75 of SEQ ID NO:19 and a last codon spanning from nucleotide 460 through nucleotide 462 of SEQ ID NO:19. The coding region encoding PCaVβ21$_{130}$ is presented herein as nCaVβ21$_{390}$, which extends from nucleotide 73 to nucleotide 462 of SEQ ID NO:19. The putative signal sequence extends from nucleotide 73 to nucleotide 114 of SEQ ID NO:19. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as PCaVβ21$_{116}$, contains about 116 amino acids, extending from residue 15 through residue 130 of SEQ ID NO:19. The nucleic acid molecule encoding PCaVβ21$_{116}$ is denoted herein as nCaVβ21$_{348}$, extending from nucleotide 115 through nucleotide 462 of SEQ ID NO:19.

Translation of SEQ ID NO:22, the coding strand of nCaVβ54$_{417}$, yields a protein of about 135 amino acids containing the beta chain V, D, and J regions, denoted herein

as PCaVβ54$_{135}$, the amino acid sequence of which is presented in SEQ ID NO:23, assuming an open reading frame having an initiation codon spanning from nucleotide 13 through nucleotide 15 of SEQ ID NO:22 and a last codon spanning from nucleotide 415 through nucleotide 417 of SEQ ID NO:22. The coding region encoding PCaVβ54$_{135}$ is presented herein as nCaVβ54$_{405}$, which extends from nucleotide 13 to nucleotide 417 of SEQ ID NO:22. The putative signal sequence extends from nucleotide 13 to nucleotide 69 of SEQ ID NO:22. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as PCaVβ54$_{116}$, contains about 116 amino acids, extending from residue 20 through residue 135 of SEQ ID NO:22. The nucleic acid molecule encoding PCaVβ54$_{116}$ is denoted herein as nCaVβ54$_{348}$, extending from nucleotide 70 through nucleotide 417 of SEQ ID NO:22.

Translation of SEQ ID NO:25, the coding strand of nCaVβ182$_{423}$, yields a protein of about 128 amino acids containing the beta chain V, D, and J regions, denoted herein as PCaVβ182$_{128}$, the amino acid sequence of which is presented in SEQ ID NO:26, assuming an open reading frame having an initiation codon spanning from nucleotide 40 through nucleotide 43 of SEQ ID NO:25 and a last codon spanning from nucleotide 421 through nucleotide 423 of SEQ ID NO:25. The coding region encoding PCaVβ182$_{128}$ is presented herein as nCaVβ182$_{384}$, which extends from nucleotide 40 to nucleotide 423 of SEQ ID NO:25. The putative signal sequence extends from nucleotide 40 to nucleotide 96 of SEQ ID NO:25. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as PCaVβ182$_{109}$, contains about 109 amino acids, extending from residue 20 through residue 128 of SEQ ID NO:25. The nucleic acid molecule encoding PCaVβ182$_{109}$ is denoted herein as nCaVβ182$_{327}$, extending from nucleotide 97 through nucleotide 423 of SEQ ID NO:25.

Translation of SEQ ID NO:28, the coding strand of nCaVβ3$_{333}$, yields a protein of about 111 amino acids containing the beta chain V region, denoted herein as PCaVβ3$_{111}$, the amino acid sequence of which is presented in SEQ ID NO:29, assuming an open reading frame having a first codon spanning from nucleotide 1 through nucleotide 3 of SEQ ID NO:28 and a last codon spanning from nucleotide 331 through

nucleotide 333 of SEQ ID NO:28. The complement of SEQ ID NO:28 is SEQ ID NO:30.

Translation of SEQ ID NO:31, the coding strand of $nCaV\beta4_{351}$, yields a protein of about 109 amino acids containing the beta chain V region, denoted herein as $PCaV\beta4_{109}$, the amino acid sequence of which is presented in SEQ ID NO:32, assuming an open reading frame having a first codon spanning from nucleotide 25 through nucleotide 27 of SEQ ID NO:31 and a last codon spanning from nucleotide 349 through nucleotide 351 of SEQ ID NO:31. The complement of SEQ ID NO:31 is SEQ ID NO:33.

Translation of SEQ ID NO:34, the coding strand of $nCaV\beta12_{339}$, yields a protein of about 111 amino acids containing the beta chain V region, denoted herein as $PCaV\beta12_{111}$, the amino acid sequence of which is presented in SEQ ID NO:35, assuming an open reading frame having a first codon spanning from nucleotide 7 through nucleotide 9 of SEQ ID NO:34 and a last codon spanning from nucleotide 337 through nucleotide 339 of SEQ ID NO:34. The complement of SEQ ID NO:34 is SEQ ID NO:35.

Translation of SEQ ID NO:37, the coding strand of $nCaV\beta72_{423}$, yields a protein of about 113 amino acids containing the beta chain V region, denoted herein as $PCaV\beta72_{113}$, the amino acid sequence of which is presented in SEQ ID NO:38, assuming an open reading frame having a first codon spanning from nucleotide 85 through nucleotide 87 of SEQ ID NO:37 and a last codon spanning from nucleotide 421 through nucleotide 423 of SEQ ID NO:37. The complement of SEQ ID NO:37 is SEQ ID NO:39.

Translation of SEQ ID NO:40, the coding strand of $nCaV\beta21_{396}$, yields a protein of about 108 amino acids containing the beta chain V region, denoted herein as $PCaV\beta21_{108}$, the amino acid sequence of which is presented in SEQ ID NO:41, assuming an open reading frame having a first codon spanning from nucleotide 73 through nucleotide 75 of SEQ ID NO:40 and a last codon spanning from nucleotide 394 through nucleotide 396 of SEQ ID NO:40. The complement of SEQ ID NO:40 is SEQ ID NO:42.

Translation of SEQ ID NO:43, the coding strand of $nCaV\beta54_{354}$, yields a protein of about 114 amino acids containing the beta chain V region, denoted herein as $PCaV\beta54_{114}$, the amino acid sequence of which is presented in SEQ ID NO:44, assuming an open reading frame having a first codon spanning from nucleotide 13 through nucleotide 15 of SEQ ID NO:43 and a last codon spanning from nucleotide 352 through nucleotide 354 of SEQ ID NO:43. The complement of SEQ ID NO:43 is SEQ ID NO:45. Translation of SEQ ID NO:46, the coding strand of $nCaV\beta182_{369}$, yields a protein of about 110 amino acids containing the beta chain V region, denoted herein as $PCaV\beta182_{110}$, the amino acid sequence of which is presented in SEQ ID NO:47, assuming an open reading frame having a first codon spanning from nucleotide 40 through nucleotide 42 of SEQ ID NO:46 and a last codon spanning from nucleotide 367 through nucleotide 369 of SEQ ID NO:46. The complement of SEQ ID NO:46 is SEQ ID NO:48.

Preferred TCR Vβ proteins of the present invention include proteins that are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to $PCaV\beta3_{127}$; are at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to $PCaV\beta4_{128}$; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more preferably at least about 70% identical to $PCaV\beta12_{134}$; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to $PCaV\beta72_{133}$; or are at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to $PCaV\beta21_{130}$. More preferred are TCR Vβ proteins comprising $PCaV\beta3_{127}$, $PCaV\beta3_{111}$, $PCaV\beta3_{110}$, $PCaV\beta4_{128}$, $PCaV\beta4_{113}$, $PCaV\beta4_{109}$, $PCaV\beta12_{134}$, $PCaV\beta12_{111}$, $PCaV\beta12_{115}$, $PCaV\beta72_{133}$, $PCaV\beta72_{113}$, $PCaV\beta72_{114}$, $PCaV\beta21_{130}$, $PCaV\beta21_{108}$, $PCaV\beta21_{116}$, $PCaV\beta54_{135}$, $PCaV\beta54_{114}$, $PCaV\beta54_{116}$, $PCaV\beta182_{128}$, $PCaV\beta182_{110}$, $PCaV\beta182_{109}$ and fragments thereof; and proteins encoded by allelic variants of nucleic acid molecules encoding proteins $PCaV\beta3_{127}$, $PCaV\beta3_{111}$, $PCaV\beta3_{110}$, $PCaV\beta4_{128}$, $PCaV\beta4_{113}$, $PCaV\beta4_{109}$, $PCaV\beta12_{134}$, $PCaV\beta12_{111}$, $PCaV\beta12_{115}$, $PCaV\beta72_{133}$, $PCaV\beta72_{113}$, $PCaV\beta72_{114}$, $PCaV\beta21_{130}$, $PCaV\beta21_{108}$, $PCaV\beta21_{116}$,

$PCaV\beta54_{135}$, $PCaV\beta54_{114}$, $PCaV\beta54_{116}$, $PCaV\beta182_{128}$, $PCaV\beta182_{110}$ and/or $PCaV\beta182_{109}$,and fragments thereof.

Other preferred TCR Vβ proteins of the present invention include proteins having amino acid sequences that are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to SEQ ID NO:2; at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to SEQ ID NO:5; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more preferably at least about 70% identical to SEQ ID NO:10; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to SEQ ID NO:15; or are at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to SEQ ID NO:20. More preferred are TCR Vβ proteins comprising amino acid sequences SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins encoded by the complement of a nucleic acid sequence including SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56; and TCR Vβ proteins encoded by allelic variants of nucleic acid molecules encoding TCR Vβ proteins having amino acid sequences SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID

NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins encoded by the complement of a nucleic acid sequence including SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56; and fragments of any of such amino acid sequences.

A preferred isolated protein of the present invention comprises a protein selected from the group consisting of:(a) an isolated protein having an amino acid sequence that is at least about 55 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:29, SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 amino acids in length; (b) an isolated protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:32, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 15 amino acids in length; (c) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:10, SEQ ID NO:35, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 25 amino acids in length; and (d) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:15, SEQ ID NO:38, SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 35 amino acids in length.

A preferred isolated protein of the present invention comprises a protein selected from the group consisting of:(a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length; (b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment that is

at least about 30 nucleotides in length; (c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and (d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

It is known in the art that there are commercially available computer programs for determining the degree of similarity between two nucleic acid sequences. These computer programs include various known methods to determine the percentage identity and the number and length of gaps between hybrid nucleic acid molecules. Preferred methods to determine the percent identity among amino acid sequences and also among nucleic acid sequences include analysis using one or more of the commercially available computer programs designed to compare and analyze nucleic acid or amino acid sequences. These computer programs include, but are not limited to, GCG™ (available from Genetics Computer Group, Madison, WI), DNAsis™ (available from Hitachi Software, San Bruno, CA) and MacVector™ (available from the Eastman Kodak Company, New Haven, CT). A preferred method to determine percent identity among amino acid sequences and also among nucleic acid sequences includes using the Compare function by maximum matching within the program DNAsis Version 2.1.

Additional preferred TCR Vβ proteins of the present invention include proteins encoded by nucleic acid molecules comprising at least a portion of $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$,$nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ and/or

nCaVβ182$_{327}$, fragments thereof, as well as TCR Vβ proteins encoded by allelic variants of such nucleic acid molecules.

Also preferred are TCR Vβ proteins encoded by nucleic acid molecules having nucleic acid sequences comprising at least a portion of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:22, SEQ ID NO:25, SEQ ID NO:28, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:37, SEQ ID NO:40, SEQ ID NO:43, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, fragments thereof, as well as allelic variants of these nucleic acid molecules.

The present invention also includes mimetopes of TCR Vβ proteins of the present invention. As used herein, a mimetope of a TCR Vβ protein of the present invention refers to any compound that is able to mimic the activity of a TCR Vβ protein of the present invention, often because the mimetope has a structure that mimics the particular TCR Vβ protein. It is to be noted that the term "a mimetope" refers to one or more or at least one mimetope. Mimetopes can be, but are not limited to: peptides that have been modified to decrease their susceptibility to degradation such as all-D retro peptides; anti-idiotypic and/or catalytic antibodies, or fragments thereof; non-proteinaceous immunogenic portions of an isolated protein (e.g., carbohydrate structures); and synthetic or natural organic molecules, including nucleic acids. Such mimetopes can be designed using computer-generated structures of proteins of the present invention. Mimetopes can also be obtained by generating random samples of molecules, such as oligonucleotides, peptides, RNA or other organic molecules, non-organic molecules and screening such samples by affinity chromatography techniques using the corresponding binding partner.

Another embodiment of the present invention includes a TCR Vβ nucleic acid molecule. It is to be noted that the term "a nucleic acid molecule homolog" refers to one or more or at least one nucleic acid molecule homologs. In accordance with the present invention, an isolated nucleic acid molecule is a nucleic acid molecule that has been removed from its natural milieu (i.e., that has been subjected to human manipulation) and can include DNA, RNA, or derivatives of either DNA or RNA. As such, "isolated" does not reflect the extent to which the nucleic acid molecule has been purified. An isolated TCR Vβ nucleic acid molecule of the present invention can be isolated from its natural source or produced using recombinant DNA technology (e.g., polymerase chain reaction (PCR) amplification or cloning) or chemical synthesis. Isolated TCR Vβ nucleic acid molecules can include, for example, natural allelic variants and nucleic acid molecules modified by nucleotide insertions, deletions, substitutions, and/or inversions in a manner such that the modifications do not substantially interfere with the nucleic acid molecule's ability to encode a TCR Vβ protein of the present invention.

A nucleic acid molecule of the present invention can include one or more regulatory regions, full-length or partial coding regions, or combinations thereof. The minimal size of a nucleic acid molecule of the present invention is a size sufficient to allow the formation of a stable hybrid with the complementary sequence of another nucleic acid molecule. As such, the minimal size of a TCR Vβ nucleic acid molecule of the present invention is from about 12 to about 18 nucleotides in length.

A TCR Vβ nucleic acid molecule homolog can be produced using a number of methods known to those skilled in the art, see, for example, Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Labs Press, *ibid.*. For example, nucleic acid molecules can be modified using a variety of techniques including, but not limited to, classic mutagenesis and recombinant DNA techniques such as site-directed mutagenesis, chemical treatment, restriction enzyme cleavage, ligation of nucleic acid fragments, PCR amplification, synthesis of oligonucleotide mixtures and ligation of mixture groups to "build" a mixture of nucleic acid molecules, and combinations thereof. Nucleic acid molecule homologs can be selected by hybridization with a TCR Vβ nucleic acid molecule or by screening the function of a protein encoded

by the nucleic acid molecule (e.g., ability to elicit an immune response against at least one epitope of a TCR Vβ protein).

An isolated nucleic acid molecule of the present invention can include a nucleic acid sequence that encodes at least one TCR Vβ protein of the present invention, examples of such proteins being disclosed herein. Although the phrase "nucleic acid molecule" primarily refers to the physical nucleic acid molecule and the phrase "nucleic acid sequence" primarily refers to the sequence of nucleotides on the nucleic acid molecule, the two phrases can be used interchangeably, especially with respect to a nucleic acid molecule, or a nucleic acid sequence, being capable of encoding a TCR Vβ protein.

A preferred nucleic acid molecule of the present invention, when administered to an animal, is capable of regulating an immune response in an animal. As will be disclosed in more detail below, such a nucleic acid molecule can be, or encode, an antisense RNA, a molecule capable of triple helix formation, a ribozyme, or other nucleic acid-based drug compound. In additional embodiments, a nucleic acid molecule of the present invention can encode an immunoregulatory protein (e.g., a cell-bound or soluble TCR Vβ protein of the present invention), the nucleic acid molecule being delivered to the animal, for example, by direct injection (i.e, as a genetic vaccine) or in a vehicle such as a recombinant virus vaccine or a recombinant cell vaccine.

One embodiment of the present invention is a TCR Vβ nucleic acid molecule comprising all or part of nucleic acid molecules $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$,$nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ and/or $nCaV\beta182_{327}$, or allelic variants of these nucleic acid molecules. Another preferred nucleic acid molecule comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27,SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID

NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof; as well as fragments thereof; as well as allelic variants of nucleic acid molecules having these nucleic acid sequences. Such nucleic acid molecules can include nucleotides in addition to those included in the SEQ ID NOs, such as, but not limited to, a full-length gene, a full-length coding region, a nucleic acid molecule encoding a fusion protein, or a nucleic acid molecule encoding a multivalent therapeutic compound.

In one embodiment, a TCR Vβ nucleic acid molecule of the present invention encodes a protein that is at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to PCaVβ3$_{127}$; are at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to PCaVβ4$_{128}$; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more preferably at least about 70% identical to PCaVβ12$_{134}$; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to PCaVβ72$_{133}$; or are at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to PCaVβ21$_{130}$. Even more preferred is a nucleic acid molecule encoding PCaVβ3$_{127}$, PCaVβ3$_{111}$, PCaVβ3$_{110}$, PCaVβ4$_{128}$, PCaVβ4$_{113}$, PCaVβ4$_{109}$, PCaVβ12$_{134}$, PCaVβ12$_{111}$, PCaVβ12$_{115}$, PCaVβ72$_{133}$, PCaVβ72$_{113}$, PCaVβ72$_{114}$, PCaVβ21$_{130}$, PCaVβ21$_{108}$, PCaVβ21$_{116}$, PCaVβ54$_{135}$,

$PCaV\beta54_{114}$, $PCaV\beta54_{116}$, $PCaV\beta182_{128}$, $PCaV\beta182_{110}$ and/or $PCaV\beta182_{109}$, fragments thereof, complements thereof, and/or an allelic variant of such a nucleic acid molecule.

In another embodiment, a TCR Vβ nucleic acid molecule of the present invention encodes a protein having an amino acid sequence that is at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to SEQ ID NO:2; are at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to SEQ ID NO:5; are at least about 57%, preferably at least about 60%, even more preferably at least about 65%, and even more preferably at least about 70% identical to SEQ ID NO:10; are at least about 65%, preferably at least about 70%, even more preferably at least about 75%, and even more preferably at least about 80% identical to SEQ ID NO:15; or at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to SEQ ID NO:20. The present invention also includes a TCR Vβ nucleic acid molecule encoding a protein having at least a portion of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins encoded by the complement of a nucleic acid sequence including SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56; fragments thereof; complements thereof, as well as allelic variants of a TCR Vβ nucleic acid molecule encoding a protein having these sequences, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

In one embodiment, a TCR Vβ nucleic acid molecule of the present invention is at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to $nCaV\beta3_{381}$; is at least

about 75%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to nCaVβ4$_{408}$; is at least about 72%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to nCaVβ12$_{408}$; is at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to nCaVβ72$_{438}$; or is at least about 38%, preferably at least about 45%, even more preferably at least about 50%, and even more preferably at least about 55% identical to nCaVβ21$_{462}$. Even more preferred is a nucleic acid molecule comprising nCaVβ3$_{381}$, nCaVβ3$_{333}$, nCaVβ3$_{330}$, nCaVβ4$_{408}$, nCaVβ4$_{384}$, nCaVβ4$_{351}$, nCaVβ4$_{339}$, nCaVβ12$_{408}$, nCaVβ12$_{402}$, nCaVβ12$_{339}$, nCaVβ12$_{345}$, nCaVβ72$_{438}$, nCaVβ72$_{399}$, nCaVβ72$_{423}$, nCaVβ72$_{342}$, nCaVβ21$_{462}$, nCaVβ21$_{390}$, nCaVβ21$_{396}$, nCaVβ21$_{348}$, nCaVβ54$_{417}$, nCaVβ54$_{405}$,nCaVβ54$_{354}$, nCaVβ54$_{348}$, nCaVβ182$_{423}$, nCaVβ182$_{384}$, nCaVβ182$_{369}$ and/or nCaVβ182$_{327}$; fragments thereof; complements thereof; as well as an allelic variant of such a nucleic acid molecule.

In another embodiment, a TCR Vβ nucleic acid molecule of the present invention comprises a nucleic acid sequence that is at least about 69%, preferably at least about 75%, even more preferably at least about 80%, and even more preferably at least about 85% identical to SEQ ID NO:1; is at least about 75%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to SEQ ID NO:4; is at least about 72%, preferably at least about 80%, even more preferably at least about 85%, and even more preferably at least about 90% identical to SEQ ID NO:9; is at least about 60%, preferably at least about 65%, even more preferably at least about 70%, and even more preferably at least about 75% identical to SEQ ID NO:98; or is at least about 38%, preferably at least about 45%, even more preferably at least about 50%, and even more preferably at least about 55% identical to SEQ ID NO:19. The present invention also includes a TCR Vβ nucleic acid molecule comprising at least a portion of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27,SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID

NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof; fragments thereof; complements thereof; as well as allelic variants of such TCR Vβ nucleic acid molecules, including nucleic acid molecules that have been modified to accommodate codon usage properties of the cells in which such nucleic acid molecules are to be expressed.

A preferred isolated nucleic acid molecule of the present invention comprises a nucleic acid sequence that hybridizes under stringent hybridization conditions to a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:100, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:24, SEQ ID NO:27, SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:45, SEQ ID NO:48, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or the complement of a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80; or fragments thereof.

A preferred isolated nucleic acid molecule of the present invention comprises a nucleic acid sequence that is any of the following: (a) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group

consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, SEQ ID NO:30 and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length; (b) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, SEQ ID NO:33, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length; (c) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, SEQ ID NO:36, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, and the complement of a nucleic acid sequence that encodes an amino acid sequence selecte from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:67, or a fragment thereof that is at least about 40 nucleotides in length; (d) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, SEQ ID NO:39, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, and the complement of a nucleic acid sequence that encodes an amino acid sequence selecte from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length; and (e) a nucleic acid sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

A preferred isolated nucleic acid molecule of the present invention comprises a nucleic acid sequence encoding a protein selected from the group consisting of: (a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length; (b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length; (c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and (d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

Another embodiment of the present invention is an isolated nucleic acid molecule selected from the group consisting of: (a) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30, or a fragment thereof, wherein said fragment has an at least a 20 contiguous nucleotide region identical in sequence to a 20 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30; (b) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the

group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, and SEQ ID NO:33, or a fragment thereof, wherein said fragment has an at least a 25 contiguous nucleotide region identical in sequence to a 25 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31 and SEQ ID NO:33; (c) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36, or a fragment thereof, wherein said fragment has an at least a 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36; and (d) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39, or a fragment thereof, wherein said fragment has an at least a 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39. The phrase, a homolog having an at least "x" contiguous nucleotide region identical in sequence to an "x" contiguous nucleotide region of a nucleic acid molecule selected from the group consisting of SEQ ID NO:"y", refers to an "x"-nucleotide in length nucleic acid molecule that is identical in sequence to an "x"-nucleotide portion of SEQ ID NO:"y", as well as to nucleic acid molecules that are longer in length than "x". The additional length may be in the form of nucleotides that extend from either the 5' or the 3' end(s) of the contiguous identical "x"-nucleotide portion. The 5' and/or 3' extensions can include one or more extensions that have no identity to an immunoregulatory molecule of the present invention, as well as extensions that show similarity or identity to cited nucleic acids sequences or portions thereof.

Knowing the nucleic acid sequences of certain TCR Vβ nucleic acid molecules of the present invention allows one skilled in the art to, for example, (a) make copies of those nucleic acid molecules, (b) obtain nucleic acid molecules including at least a

portion of such nucleic acid molecules (e.g., nucleic acid molecules including full-length genes, full-length coding regions, regulatory control sequences, truncated coding regions), and (c) obtain other TCR Vβ nucleic acid molecules. Such nucleic acid molecules can be obtained in a variety of ways including screening appropriate expression libraries with antibodies of the present invention; traditional cloning techniques using oligonucleotide probes of the present invention to screen appropriate libraries; and PCR amplification of appropriate libraries or DNA using oligonucleotide primers of the present invention. Preferred libraries to screen or from which to amplify nucleic acid molecules include mammalian cDNA libraries as well as genomic DNA libraries. Similarly, preferred DNA sources from which to amplify nucleic acid molecules include mammalian cDNA and genomic DNA. Techniques to clone and amplify genes are disclosed, for example, in Sambrook et al., *ibid.*

The present invention also includes nucleic acid molecules that are oligonucleotides capable of hybridizing, under stringent hybridization conditions, with complementary regions of other, preferably longer, nucleic acid molecules of the present invention such as those comprising TCR Vβ nucleic acid molecules. Oligonucleotides of the present invention can be RNA, DNA, or derivatives of either. The minimum size of such oligonucleotides is the size required for formation of a stable hybrid between an oligonucleotide and a complementary sequence on a nucleic acid molecule of the present invention. A preferred oligonucleotide of the present invention has a maximum size of about 100 nucleotides. A preferred oligonucleotide of the present invention has a minimum size of about 12 nucleotides. Preferably, an oligonucleotide of the present invention has a size from about 12 nucleotides to about 30 nucleotides and more preferably from about 15 nucleotides to about 25 nucleotides.

A preferred isolated oligonucleotide of the present invention comprises a unique nucleic acid sequence within a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27,SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID

NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof; and a homolog thereof.

The present invention includes oligonucleotides that can be used, for example, as probes to identify nucleic acid molecules, primers to produce nucleic acid molecules, or therapeutic reagents to inhibit TCR Vβ protein production or activity (e.g., as antisense-, triplex formation-, ribozyme- and/or RNA drug-based reagents). The present invention also includes the use of such oligonucleotides to protect animals from disease using one or more of such technologies. Appropriate oligonucleotide-containing therapeutic compositions can be administered to an animal using techniques known to those skilled in the art.

Preferred oligonucleotides of the present invention include oligonucleotides comprising a unique nucleic acid sequence, as defined herein, within a nucleic acid molecule of the present invention or homologs thereof. Preferred homologs of an oligonucleotide are capable of priming a nucleic acid sequence.

One embodiment of the present invention includes a recombinant vector, which includes at least one isolated nucleic acid molecule of the present invention, inserted into any vector capable of delivering the nucleic acid molecule into a host cell. Such a vector contains heterologous nucleic acid sequences, that is nucleic acid sequences that are not naturally found adjacent to nucleic acid molecules of the present invention and that preferably are derived from a species other than the species from which the nucleic acid molecule(s) are derived. The vector can be either RNA or DNA, either prokaryotic or eukaryotic, and typically is a virus or a plasmid. Recombinant vectors can be used in the

cloning, sequencing, and/or otherwise manipulating of TCR Vβ nucleic acid molecules of the present invention.

One type of recombinant vector, referred to herein as a recombinant molecule, comprises a nucleic acid molecule of the present invention operatively linked to an expression vector. The phrase operatively linked refers to insertion of a nucleic acid molecule into an expression vector in a manner such that the molecule is able to be expressed when transformed into a host cell. As used herein, an expression vector is a DNA or RNA vector that is capable of transforming a host cell and of effecting expression of a specified nucleic acid molecule. Preferably, the expression vector is also capable of replicating within the host cell. Expression vectors can be either prokaryotic or eukaryotic, and are typically viruses or plasmids. Expression vectors of the present invention include any vectors that function (i.e., direct gene expression) in recombinant cells of the present invention, including in bacterial, fungal, parasite, insect, other animal, and plant cells. Preferred expression vectors of the present invention can direct gene expression in bacterial, yeast, insect and mammalian cells, and more preferably in the cell types disclosed herein

In particular, expression vectors of the present invention contain regulatory sequences such as transcription control sequences, translation control sequences, origins of replication, and other regulatory sequences that are compatible with the recombinant cell and that control the expression of nucleic acid molecules of the present invention. In particular, recombinant molecules of the present invention include transcription control sequences. Transcription control sequences are sequences which control the initiation, elongation, and termination of transcription. Particularly important transcription control sequences are those which control transcription initiation, such as promoter, enhancer, operator and repressor sequences. Suitable transcription control sequences include any transcription control sequence that can function in at least one of the recombinant cells of the present invention. A variety of such transcription control sequences are known to those skilled in the art. Preferred transcription control sequences include those which function in bacterial, yeast, helminth or other endoparasite, or insect and mammalian cells, such as, but not limited to, *tac*, *lac*, *trp*, *trc*, oxy-pro, omp/lpp, rrnB, bacteriophage lambda (such as lambda p_L and lambda p_R and

fusions that include such promoters), bacteriophage T7, T7*lac*, bacteriophage T3, bacteriophage SP6, bacteriophage SP01, metallothionein, alpha-mating factor, *Pichia* alcohol oxidase, alphavirus subgenomic promoter, antibiotic resistance gene, baculovirus, *Heliothis zea* insect virus, vaccinia virus, herpesvirus, raccoon poxvirus, other poxvirus, adenovirus, cytomegalovirus (such as immediate early promoter), simian virus 40, retrovirus, actin, retroviral long terminal repeat, Rous sarcoma virus, heat shock, phosphate and nitrate transcription control sequences as well as other sequences capable of controlling gene expression in prokaryotic or eukaryotic cells. Additional suitable transcription control sequences include tissue-specific promoters and enhancers as well as lymphokine-inducible promoters (e.g., promoters inducible by interferons or interleukins). Transcription control sequences of the present invention can also include naturally occurring transcription control sequences naturally associated with mammals, such as canine or feline transcription control sequences.

Suitable and preferred nucleic acid molecules to include in recombinant vectors of the present invention are as disclosed herein. Preferred nucleic acid molecules to include in recombinant vectors, and particularly in recombinant molecules, include $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$, $nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ and/or $nCaV\beta182_{327}$.

Recombinant molecules of the present invention may also (a) contain secretory signals (i.e., signal segment nucleic acid sequences) to enable an expressed TCR Vβ protein of the present invention to be secreted from the cell that produces the protein and/or (b) contain fusion sequences which lead to the expression of nucleic acid molecules of the present invention as fusion proteins. Examples of suitable signal segments include any signal segment capable of directing the secretion of a protein of the present invention. Preferred signal segments include, but are not limited to, tissue plasminogen activator (t-PA), interferon, interleukin, growth hormone, histocompatibility and viral envelope glycoprotein signal segments. Suitable fusion segments encoded by fusion segment nucleic acids are disclosed herein. In addition, a

nucleic acid molecule of the present invention can be joined to a fusion segment that directs the encoded protein to the proteosome, such as a ubiquitin fusion segment. Eukaryotic recombinant molecules may also include intervening and/or untranslated sequences surrounding and/or within the nucleic acid sequences of nucleic acid molecules of the present invention.

Another embodiment of the present invention includes a recombinant cell comprising a host cell transformed with one or more recombinant molecules of the present invention. Transformation of a nucleic acid molecule into a cell can be accomplished by any method by which a nucleic acid molecule can be inserted into the cell. Transformation techniques include, but are not limited to, transfection, electroporation, microinjection, lipofection, adsorption, and protoplast fusion. A recombinant cell may remain unicellular or may grow into a tissue, organ or a multicellular organism. Transformed nucleic acid molecules of the present invention can remain extrachromosomal or can integrate into one or more sites within a chromosome of the transformed (i.e., recombinant) cell in such a manner that their ability to be expressed is retained. Preferred nucleic acid molecules with which to transform a cell include TCR Vβ nucleic acid molecules disclosed herein. Particularly preferred nucleic acid molecules with which to transform a cell include $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$, $nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ and/or $nCaV\beta182_{327}$.

Suitable host cells to transform include any cell that can be transformed with a nucleic acid molecule of the present invention. Host cells can be either untransformed cells or cells that are already transformed with at least one nucleic acid molecule (e.g., nucleic acid molecules encoding one or more proteins of the present invention and/or other proteins useful in the production of multivalent vaccines). Host cells of the present invention either can be endogenously (i.e., naturally) capable of producing TCR Vβ proteins of the present invention or can be capable of producing such proteins after being transformed with at least one nucleic acid molecule of the present invention. Host cells

of the present invention can be any cell capable of producing at least one protein of the present invention, and include bacterial, fungal (including yeast), parasite (including helminth, protozoa and ectoparasite), other insect, other animal and plant cells. Preferred host cells include bacterial, mycobacterial, yeast, helminth, insect and mammalian cells. More preferred host cells include *Salmonella*, *Escherichia*, *Bacillus*, *Listeria*, *Pichia*, *Saccharomyces*, *Spodoptera*, *Mycobacteria*, *Trichoplusia*, BHK (baby hamster kidney) cells, MDCK cells (Madin-Darby canine kidney cell line), CRFK cells (Crandell feline kidney cell line), CV-1 cells (African monkey kidney cell line used, for example, to culture raccoon poxvirus), COS (e.g., COS-7) cells, chinese hamster ovary (CHO) cells, Ltk cells and Vero cells. Particularly preferred host cells are *Escherichia coli*, including *E. coli* K-12 derivatives; *Salmonella typhi*; *Salmonella typhimurium*, including attenuated strains such as UK-1 $_0$3987 and SR-11 $_0$4072; *Spodoptera frugiperda*; *Trichoplusia ni*; BHK cells; MDCK cells; CRFK cells; CV-1 cells; COS cells; Vero cells; and non-tumorigenic mouse myoblast G8 cells (e.g., ATCC CRL 1246). Additional appropriate mammalian cell hosts include other kidney cell lines, other fibroblast cell lines (e.g., human, murine or chicken embryo fibroblast cell lines), myeloma cell lines, Chinese hamster ovary cells, mouse NIH/3T3 cells, LMTK^{31} cells and/or HeLa cells. In one embodiment, the proteins may be expressed as heterologous proteins in myeloma cell lines employing immunoglobulin promoters.

A recombinant cell is preferably produced by transforming a host cell with one or more recombinant molecules, each comprising one or more nucleic acid molecules of the present invention operatively linked to an expression vector containing one or more transcription control sequences, examples of which are disclosed herein.

A recombinant cell of the present invention includes any cell transformed with at least one of any nucleic acid molecule of the present invention. Suitable and preferred nucleic acid molecules as well as suitable and preferred recombinant molecules with which to transfer cells are disclosed herein.

It is to be noted that the term "a recombinant molecule", "a host cell" or "a recombinant cell" refers to one or more or at least one recombinant molecule, host cell or recombinant cell, respectively.

Recombinant cells of the present invention can also be co-transformed with one or more recombinant molecules including TCR Vβ nucleic acid molecules encoding one or more proteins of the present invention and one or more other nucleic acid molecules encoding other therapeutic compounds, as disclosed herein (e.g., to produce multivalent vaccines).

Recombinant DNA technologies can be used to improve expression of transformed nucleic acid molecules by manipulating, for example, the number of copies of the nucleic acid molecules within a host cell, the efficiency with which those nucleic acid molecules are transcribed, the efficiency with which the resultant transcripts are translated, and the efficiency of post-translational modifications. Recombinant techniques useful for increasing the expression of nucleic acid molecules of the present invention include, but are not limited to, operatively linking nucleic acid molecules to high-copy number plasmids, integration of the nucleic acid molecules into one or more host cell chromosomes, addition of vector stability sequences to plasmids, substitutions or modifications of transcription control signals (e.g., promoters, operators, enhancers), substitutions or modifications of translational control signals (e.g., ribosome binding sites, Shine-Dalgarno sequences), modification of nucleic acid molecules of the present invention to correspond to the codon usage of the host cell, deletion of sequences that destabilize transcripts, and use of control signals that temporally separate recombinant cell growth from recombinant enzyme production during fermentation. The activity of an expressed recombinant protein of the present invention may be improved by fragmenting, modifying, or derivatizing nucleic acid molecules encoding such a protein.

Isolated TCR Vβ proteins of the present invention can be produced in a variety of ways, including production and recovery of natural proteins, production and recovery of recombinant proteins, and chemical synthesis of the proteins. In one embodiment, an isolated protein of the present invention is produced by culturing a cell capable of expressing the protein under conditions effective to produce the protein, and recovering the protein. A preferred cell to culture is a recombinant cell of the present invention. Effective culture conditions include, but are not limited to, effective media, bioreactor, temperature, pH and oxygen conditions that permit protein production. An effective, medium refers to any medium in which a cell is cultured to produce a TCR Vβ protein

of the present invention. Such medium typically comprises an aqueous medium having assimilable carbon, nitrogen and phosphate sources, and appropriate salts, minerals, metals and other nutrients, such as vitamins. Cells of the present invention can be cultured in conventional fermentation bioreactors, shake flasks, test tubes, microtiter dishes, and petri plates. Culturing can be carried out at a temperature, pH and oxygen content appropriate for a recombinant cell. Such culturing conditions are within the expertise of one of ordinary skill in the art.

Depending on the vector and host system used for production, resultant proteins of the present invention may either remain within the recombinant cell; be secreted into the fermentation medium; be secreted into a space between two cellular membranes, such as the periplasmic space in *E. coli*; or be retained on the outer surface of a cell or viral membrane.

The phrase "recovering the protein", as well as similar phrases, refers to collecting the whole fermentation medium containing the protein and need not imply additional steps of separation or purification. Proteins of the present invention can be purified using a variety of standard protein purification techniques, such as, but not limited to, affinity chromatography, ion exchange chromatography, filtration, electrophoresis, hydrophobic interaction chromatography, gel filtration chromatography, reverse phase chromatography, concanavalin A chromatography, chromatofocusing and differential solubilization. Proteins of the present invention are preferably retrieved in "substantially pure" form. As used herein, "substantially pure" refers to a purity that allows for the effective use of the protein as a therapeutic composition or diagnostic. A therapeutic composition for animals, for example, should exhibit no substantial toxicity and preferably should be capable of stimulating the production of antibodies in a treated animal.

The present invention also includes isolated (i.e., removed from their natural milieu) antibodies that selectively bind to a TCR Vβ protein of the present invention or a mimetope thereof (e.g., anti-TCR Vβ antibodies). As used herein, the term "selectively binds to" a TCR Vβ protein refers to the ability of antibodies of the present invention to preferentially bind to specified proteins and mimetopes thereof of the present invention. Binding can be measured using a variety of methods standard in the art including

enzyme immunoassays (e.g., ELISA), immunoblot assays, etc.; see, for example, Sambrook et al., *ibid.*, and Harlow, et al., 1988, *Antibodies, a Laboratory Manual*, Cold Spring Harbor Labs Press; Harlow et al., *ibid.* An anti- TCR Vβ antibody of the present invention preferably selectively binds to a TCR Vβ protein in such a way as to inhibit the function of that protein.

Isolated antibodies of the present invention can include antibodies in serum, or antibodies that have been purified to varying degrees. Antibodies of the present invention can be polyclonal or monoclonal, or can be functional equivalents such as antibody fragments and genetically-engineered antibodies, including single chain antibodies or chimeric antibodies that can bind to one or more epitopes.

A preferred method to produce antibodies of the present invention includes (a) administering to an animal an effective amount of a protein, peptide or mimetope thereof of the present invention to produce the antibodies and (b) recovering the antibodies. In another method, antibodies of the present invention are produced recombinantly using techniques as heretofore disclosed to produce TCR Vβ proteins of the present invention. Antibodies raised against defined proteins or mimetopes can be advantageous because such antibodies are not substantially contaminated with antibodies against other substances that might otherwise cause interference in a diagnostic assay or side effects if used in a therapeutic composition.

Antibodies of the present invention have a variety of potential uses that are within the scope of the present invention. For example, such antibodies can be used (a) as reagents in assays to detect TCR Vβ protein, (b) as reagents in assays to modulate cellular activity through a TCR Vβ protein (e.g., mimicking ligand binding to TCR Vβ protein), and/or (c) as tools to screen expression libraries and/or to recover desired proteins of the present invention from a mixture of proteins and other contaminants. Furthermore, antibodies of the present invention can be used to target compounds (e.g., nucleic acid molecules, drugs or proteins) to antigen presenting cells. Targeting can be accomplished by conjugating (i.e., stably joining) such antibodies to the compounds using techniques known to those skilled in the art. Suitable compounds are known to those skilled in the art.

One embodiment of the present invention is a therapeutic composition that, when administered to an animal in an effective manner, is capable of regulating an immune response in an animal. Therapeutic compositions of the present invention include at least one of the following therapeutic compounds: an isolated TCR Vβ protein of the present invention or a mimetope thereof, an isolated TCR Vβ nucleic acid molecule of the present invention, an isolated antibody that selectively binds to a TCR Vβ protein of the present invention, an inhibitor of TCR Vβ function identified by its ability to bind to a TCR Vβ protein of the present invention and inhibit binding of a TCR Vβ protein to MHC, and a mixture thereof (i.e., combination of at least two of the compounds). As used herein, a therapeutic compound refers to a compound that, when administered to an animal in an effective manner, is able to treat, ameliorate, and/or prevent a disease. Examples of proteins, nucleic acid molecules, antibodies and inhibitors of the present invention are disclosed herein.

The present invention also includes a therapeutic composition comprising at least one TCR Vβ-based compound of the present invention in combination with at least one additional therapeutic compound. Examples of such compounds are disclosed herein.

Therapeutic compositions of the present invention can be administered to any animal susceptible to such therapy, preferably to mammals, and more preferably to dogs.

A therapeutic composition of the present invention is administered to an animal in an effective manner such that the composition is capable of regulating an immune response in that animal. Therapeutic compositions of the present invention can be administered to animals prior to onset of a disease (i.e., as a preventative vaccine) and/or can be administered to animals after onset of a disease in order to treat the disease (i.e., as a therapeutic vaccine). Preferred diseases to prevent or treat include autoimmune diseases, allergic reactions, infectious diseases and cancer.

Therapeutic compositions of the present invention can be formulated in an excipient that the animal to be treated can tolerate. Examples of such excipients include water, saline, Ringer's solution, dextrose solution, Hank's solution, and other aqueous physiologically balanced salt solutions. Nonaqueous vehicles, such as fixed oils, sesame oil, ethyl oleate, or triglycerides may also be used. Other useful formulations include

suspensions containing viscosity enhancing agents, such as sodium carboxymethylcellulose, sorbitol, or dextran. Excipients can also contain minor amounts of additives, such as substances that enhance isotonicity and chemical stability. Examples of buffers include phosphate buffer, bicarbonate buffer and Tris buffer, while examples of preservatives include thimerosal, o-cresol, formalin and benzyl alcohol. Standard formulations can either be liquid injectables or solids which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise dextrose, human serum albumin, preservatives, etc., to which sterile water or saline can be added prior to administration.

In one embodiment of the present invention, a therapeutic composition can include an adjuvant. Adjuvants are agents that are capable of enhancing the immune response of an animal to a specific antigen. Suitable adjuvants include, but are not limited to, cytokines, chemokines, and compounds that induce the production of cytokines and chemokines (e.g., Flt-3 ligand, granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), colony stimulating factor (CSF), erythropoietin (EPO), interleukin 2 (IL-2), interleukin-3 (IL-3), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 8 (IL-8), interleukin 10 (IL-10), interleukin 12 (IL-12), interferon gamma, interferon gamma inducing factor I (IGIF), transforming growth factor beta, RANTES (regulated upon activation, normal T cell expressed and presumably secreted), macrophage inflammatory proteins (e.g., MIP-1 alpha and MIP-1 beta), and Leishmania elongation initiating factor (LEIF)); bacterial components (e.g., endotoxins, in particular superantigens, exotoxins and cell wall components); aluminum-based salts; calcium-based salts; silica; polynucleotides; toxoids; serum proteins, viral coat proteins; block copolymer adjuvants (e.g., Hunter's Titermax™ adjuvant (Vaxcel™, Inc. Norcross, GA), Ribi adjuvants (Ribi ImmunoChem Research, Inc., Hamilton, MT); and saponins and their derivatives (e.g., Quil A (Superfos Biosector A/S, Denmark). Protein adjuvants of the present invention can be delivered in the form of the protein themselves or of nucleic acid molecules encoding such proteins using the methods described herein. A therapeutic composition can contain one or more adjuvants.

In one embodiment of the present invention, a therapeutic composition can include a carrier. Carriers include compounds that increase the half-life of a therapeutic composition in the treated animal. Suitable carriers include, but are not limited to, polymeric controlled release vehicles, biodegradable implants, liposomes, bacteria, viruses, other cells, oils, esters, and glycols. A therapeutic composition can contain one or more carriers.

One embodiment of the present invention is a controlled release formulation that is capable of slowly releasing a composition of the present invention into an animal. As used herein, a controlled release formulation comprises a composition of the present invention in a controlled release vehicle. Suitable controlled release vehicles include, but are not limited to, biocompatible polymers, other polymeric matrices, capsules, microcapsules, microparticles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Other controlled release formulations of the present invention include liquids that, upon administration to an animal, form a solid or a gel *in situ*. Preferred controlled release formulations are biodegradable (i.e., bioerodible).

A preferred controlled release formulation of the present invention is capable of releasing a composition of the present invention into the blood of the treated animal at a constant rate sufficient to attain therapeutic dose levels of the composition to regulate an immune response in an animal. The therapeutic composition is preferably released over a period of time ranging from about 1 to about 12 months. A controlled release formulation of the present invention is capable of effecting a treatment preferably for at least about 1 month, more preferably for at least about 3 months, even more preferably for at least about 6 months, even more preferably for at least about 9 months, and even more preferably for at least about 12 months.

Therapeutic compositions of the present invention can be administered to animals prior to and/or after onset of disease. Acceptable protocols to administer therapeutic compositions in an effective manner include individual dose size, number of doses, frequency of dose administration, and mode of administration. Determination of such protocols can be accomplished by those skilled in the art. A suitable single dose is a dose that is capable of regulating the immune response in an animal when administered

one or more times over a suitable time period. For example, a preferred single dose of a protein, mimetope or antibody therapeutic composition is from about 1 microgram (g) to about 10 milligrams (mg) of the therapeutic composition per kilogram body weight of the animal. Booster vaccinations can be administered from about 2 weeks to several years after the original administration. Booster administrations preferably are administered when the immune response of the animal becomes insufficient to protect the animal from disease. A preferred administration schedule is one in which from about 10 g to about 1 mg of the therapeutic composition per kg body weight of the animal is administered from about one to about two times over a time period of from about 2 weeks to about 12 months. Modes of administration can include, but are not limited to, subcutaneous, intradermal, intravenous, intranasal, intraoccular, oral, transdermal and intramuscular routes.

According to one embodiment, a nucleic acid molecule of the present invention can be administered to an animal in a fashion to enable expression of that nucleic acid molecule into a therapeutic protein or therapeutic RNA (e.g., antisense RNA, ribozyme, triple helix forms or RNA drug) in the animal. Nucleic acid molecules can be delivered to an animal in a variety of methods including, but not limited to, (a) administering a naked (i.e., not packaged in a viral coat or cellular membrane) nucleic acid as a genetic vaccine (e.g., as naked DNA or RNA molecules, such as is taught, for example in Wolff et al., 1990, *Science 247*, 1465-1468) or (b) administering a nucleic acid molecule packaged as a recombinant virus vaccine or as a recombinant cell vaccine (i.e., the nucleic acid molecule is delivered by a viral or cellular vehicle). One or more nucleic acid molecules can be delivered to an animal.

A genetic (i.e., naked nucleic acid) vaccine of the present invention includes a nucleic acid molecule of the present invention and preferably includes a recombinant molecule of the present invention that preferably is replication, or otherwise amplification, competent. A genetic vaccine of the present invention can comprise one or more nucleic acid molecules of the present invention in the form of, for example, a dicistronic recombinant molecule. Preferred genetic vaccines include at least a portion of a viral genome (i.e., a viral vector). Preferred viral vectors include those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, picornaviruses, and retroviruses,

with those based on alphaviruses (such as sindbis or Semliki forest virus), species-specific herpesviruses and poxviruses being particularly preferred. Any suitable transcription control sequence can be used, including those disclosed as suitable for protein production. Particularly preferred transcription control sequences include cytomegalovirus immediate early (preferably in conjunction with Intron-A), Rous sarcoma virus long terminal repeat, and tissue-specific transcription control sequences, as well as transcription control sequences endogenous to viral vectors if viral vectors are used. The incorporation of a "strong" polyadenylation signal is also preferred.

Genetic vaccines of the present invention can be administered in a variety of ways, with intramuscular, subcutaneous, intradermal, transdermal, intranasal and oral routes of administration being preferred. A preferred single dose of a genetic vaccine ranges from about 1 nanogram (ng) to about 600 g, depending on the route of administration and/or method of delivery, as can be determined by those skilled in the art. Suitable delivery methods include, for example, by injection, as drops, aerosolized and/or topically. Genetic vaccines of the present invention can be contained in an aqueous excipient (e.g., phosphate buffered saline) alone or in a carrier (e.g., lipid-based vehicles).

A recombinant virus vaccine of the present invention includes a recombinant molecule of the present invention that is packaged in a viral coat and that can be expressed in an animal after administration. Preferably, the recombinant molecule is packaging- or replication-deficient and/or encodes an attenuated virus. A number of recombinant viruses can be used, including, but not limited to, those based on alphaviruses, poxviruses, adenoviruses, herpesviruses, picornaviruses, and retroviruses. Preferred recombinant virus vaccines are those based on alphaviruses (such as Sindbis virus), raccoon poxviruses, species-specific herpesviruses and species-specific poxviruses. An example of methods to produce and use alphavirus recombinant virus vaccines are disclosed in PCT Publication No. WO 94/17813, by Xiong et al., published August 18, 1994.

When administered to an animal, a recombinant virus vaccine of the present invention infects cells within the immunized animal and directs the production of a therapeutic protein or RNA nucleic acid molecule that is capable of protecting the

animal from disease caused by a parasitic helminth as disclosed herein. For example, a recombinant virus vaccine comprising a TCR Vβ nucleic acid molecule of the present invention is administered according to a protocol that results in the regulation of an immune response in an animal. A preferred single dose of a recombinant virus vaccine of the present invention is from about 1 x 10^4 to about 1 x 10^8 virus plaque forming units (pfu) per kilogram body weight of the animal. Administration protocols are similar to those described herein for protein-based vaccines, with subcutaneous, intramuscular, intranasal, intraoccular and oral administration routes being preferred. One or more recombinant virus vaccines can be delivered to an animal.

A recombinant cell vaccine of the present invention includes recombinant cells of the present invention that express at least one protein of the present invention. Preferred recombinant cells for this embodiment include *Salmonella*, *E. coli*, *Listeria*, *Mycobacterium*, *S. frugiperda*, yeast, (including *Saccharomyces cerevisiae and Pichia pastoris*), BHK, CV-1, myoblast G8, COS (e.g., COS-7), Vero, MDCK and CRFK recombinant cells. Recombinant cell vaccines of the present invention can be administered in a variety of ways but have the advantage that they can be administered orally, preferably at doses ranging from about 10^8 to about 10^{12} cells per kilogram body weight. Administration protocols are similar to those described herein for protein-based vaccines. Recombinant cell vaccines can comprise whole cells, cells stripped of cell walls or cell lysates.

The efficacy of a therapeutic composition of the present invention to regulate the immune response in an animal can be tested in a variety of ways including, but not limited to, detection of cellular immunity within the treated animal, determination of T cell activity (helper or cytotoxic T cell activity), identification of T cell repertoire, detection of immunoregulatory cytokines, e.g., IL-2, IL-4, IL-10, IL-12, levels, detection of antibody levels, determine tumor development or challenge of the treated animal with an infectious agent to determine whether the treated animal is resistant to disease. In one embodiment, therapeutic compositions can be tested in animal models such as mice. Such techniques are known to those skilled in the art.

According to the present invention, a therapeutic composition is used to treat a disease requiring immunological regulation, such as cancer, infectious diseases,

autoimmune diseases or allergy. Suitable cancers to treat include lymphomas or leukemias. Suitable infectious diseases to treat include diseases caused by viral, bacterial, yeast, fungal or parasitic infection. Suitable autoimmune diseases to treat include: autoimmune skin diseases, e.g. pemphigus foliaceous, pemphigus vulgaris, pemphigus vegetans, pemphigus erythematosus, bollous pemphigoid, discoid lupus, dermatomyositis or subcorneal pustular dermatosis; blood disorders, e.g. autoimmune hemolytic anemia, immune-mediated thrombocytopenia, aplstic anemia, pure red cell aplasia or immune mediated neutropenia; endocrine dysfuntion, e.g. lymphocytic thyroditis, diabetes, hypoadrenocorticism or hypoparathyroidism; multi-system dysfunction, e.g. systemic lupus erythematosus or Sjogren's syndrome; neurologic dysfunction, e.g. myasthenia gravis, distemper and rabies post vaccinal encephalopathy or acute polyradiculoneuritis; or musculoskeletal disease, e.g. rheumatoid arthritis, idiopathic polyarthritis, plasmacytic-lymphocytic arthritis or polymyosutus. Suitable allergies to treat include allergic dermatitis, atopic dermatitis, allergic rhinitis or allergic bronchitis.

One therapeutic composition of the present invention includes a TCR Vß protein of the present invention, or a portion of such TCR Vß protein that elicits a cytotoxic T cell response against a T cell bearing the TCR Vß protein. A preferred TCR Vß protein comprises a soluble form of a TCR Vß protein of the present invention, with a peptide of a TCR Vß protein being more preferred. A preferred TCR Vß peptide is from about 5 to about 50 residues, more preferably from about 10 to about 40 residues and even more preferably from about 12 to about 30 residue in length. One or more TCR Vß proteins of the present invention, or portions of such TCR Vß proteins can be used in a therapeutic composition.

According to the present invention, a therapeutic composition comprising a TCR Vß peptide, e.g. a portion of a polypeptide, can be delivered to an animal as a peptide or in the form of DNA encoding such peptide. A TCR Vß peptide of the present invention can be linked to another molecule to assist in the delivery of the peptide to an animal. Preferably, a TCR Vß peptide of the present invention is administered systemically to an animal. One or more peptides can be used in a therapeutic composition.

Another therapeutic composition of the present invention includes an inhibitory compound that inhibits a TCR Vß protein from binding to MHC. An inhibitory compound is capable of substantially interfering with the function of a TCR Vß protein susceptible to inhibition. For example, an inhibitory compound is administered in an amount and manner that inhibits an immune response that is sufficient to treat an animal for a disease that requires downregulation of an immune response. One or more inhibitors can be used in a therapeutic composition.

Suitable inhibitory compounds include compounds that prevent the activation of an immunoregulatory cell through TCR Vß by, for example, interfering with the binding of TCR Vß protein to MHC by binding to either the TCR Vß protein or MHC. An example of an inhibitory compound is an antibody of the present invention, administered to an animal in an effective manner; i.e., an antibody of the present invention, is administered in an amount so as to be present in the animal at a titer that is sufficient, upon interaction of that antibody with a native TCR Vß protein, to decrease TCR Vß activity in an animal, at least temporarily. Oligonucleotide nucleic acid molecules of the present invention can also be administered in an effective manner, thereby reducing expression of TCR Vß proteins in order to interfere with TCR Vß activity targeted in accordance with the present invention. Peptides of TCR Vß proteins of the present invention can also be administered in an effective manner, thereby reducing binding of TCR Vß proteins to MHC in order to interfere with TCR Vß activity targeted in accordance with the present invention. Preferably, an inhibitory compound is derived from a TCR Vß protein of the present invention.

An inhibitory compound of TCR Vß function can be identified using TCR Vß proteins of the present invention. One embodiment of the present invention is a method to identify a compound capable of inhibiting TCR Vß function. Such a method includes the steps of: (a) contacting (e.g., combining, mixing) an isolated TCR Vß protein of the present invention, with a putative inhibitory compound under conditions in which, in the absence of the compound, the protein binds to a protein including MHC, and (b) determining if the putative inhibitory compound inhibits the binding of TCR Vß to MHC. Putative inhibitory compounds to screen include small organic molecules, antibodies (including mimetopes thereof), and ligand analogs. Such compounds can

also be screened to identify those compounds that are substantially not toxic to a recipient animal.

One embodiment of the present invention is a method to detect expansion of T cells in an animal. The present method utilizes the discovery by the inventors of unique sequences in a TCR Vß and more particularly in the V region of a TCR Vß that function, or can be used, as markers for T cells. As used herein, the term "unique sequences" refers to nucleic acid or amino acid sequences that are present in one TCR Vß nucleic acid molecule or TCR Vß protein, but not in another TCR Vß nucleic acid molecule or TCR Vß protein, respectively. Thus, a unique sequence differentiates one TCR Vß nucleic acid molecule or TCR Vß protein of the present invention from another TCR Vß nucleic acid molecule or TCR Vß protein, respectively. For example, a unique sequence within hcVβ3, is not found within hcVβ4, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182, and a unique sequence within hcVβ4, is not found within hcVβ3, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182, and so on. A unique sequence of the present invention can be used to detect expansion of T cells by, for example, determining the presence or absence of any one or more unique sequences, determining increased or decreased levels of molecules carrying one or more unique sequences compared with other unique sequences in the same animal and/or a different animal, or comparing levels of different TCR Vß proteins in an animal.

It is within the scope of the present invention that any unique sequence present in a TCR Vß sequence of the present invention can be used in the practice of the present method, including those identified herein and those which will be identified based on the sequences of nucleic acid molecules or proteins disclosed herein. Preferably, unique sequences of the present invention include those sequences located within about the first 200 nucleotides or about the first 70 residues of the 5' or amino terminus of a nucleic acid molecule or a protein. The suitable length of a unique sequence depends upon the reagent used to detect the presence of the unique sequence. For example, a suitable length of a unique sequence is from about 15 to about 30 nucleotides if the detection reagent is a DNA primer. Alternatively, a suitable length of a unique sequence is from about 50 to about 300 nucleotides if the detection reagent is a DNA hybridization probe. Alternatively, a suitable length of a unique sequence is at least about 5 amino acids if the

detection reagent is an antibody. In addition, one or more unique sequences can be identified, and one or more reagents can be used to identify such sequences, using a method of the present invention.

Any method of the present invention can be used to determine the presence, absence, amount or ratio of TCR Vß's of the present invention in an animal to determine T cell expansion and/or diagnose an abnormal state or a specific disease. Typically, numbers of T cells in an animal are regulated. Expansion of total T cell numbers, or of a particular T cell clone, can represent an abnormal state or disease. For example, a particular T cell clone is expanded in a T cell lymphoma or leukemia. Thus, information derived using the present methods is particularly useful because the inventors have discovered the seven different TCR Vß proteins disclosed herein which can comprise at least about 95% of the TCR Vß repertoire in canids. The discovery of the existence of a small repertoire of TCR Vß proteins enables the production of appropriate reagents that detect a substantial amount of T cell receptors in an animal. The reagents can be used to correlate T cell expansion with a specific disease by comparing results obtained using samples from normal animals compared with animals having or suspected of having a disease. Thus, any diagnostic method of the present invention is useful for determining if an animal is susceptible to, has or is in remission from a disease.

According to the present invention, T cell expansion is determined by detecting increased levels of one or more specific TCR Vß molecules in a tissue sample isolated from an animal. Increased levels of TCR Vß molecules can be determined by comparing levels of two or more different TCR Vß molecules in a tissue sample isolated from one animal, or levels of one or more TCR Vß molecules in tissue samples from two or more different animals. Total amounts or ratios of particular TCR Vß molecules can be determined by one of skill in the art depending upon the method used to detect the presence of a TCR Vß molecule in a sample. Preferably, a ratio illustrative of increased levels of a particular TCR Vß molecule is from about 2-fold to about 5-fold, more preferably from about 5-fold to about 25, and more preferably 10-fold more of one particular TCR Vß molecule compared with another sample of the same TCR Vß molecule or a different TCR Vß molecule. Methods to determine ratios are known to

those in the art and include, for example, densitometry, spectrophotometry or determining counts per minute of isotopes.

One embodiment of the present invention is a method to detect expansion of T cells in an animal comprising detecting the presence of one or more T cell receptors having unique nucleic acid sequences within hcVβ3, hcVβ4, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182 nucleic acid molecules or hcVβ3, hcVβ4, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182 proteins by forming detectable products, wherein the increased level of a detectable product compared with another detectable product indicates expansion of the T cells. According to the present method, a suitable sample containing T cells is isolated from an animal. Samples containing T cell receptors can be isolated from the same or different animals. Control samples can be obtained from the same or different animals. The sample is contacted under appropriate conditions with one or more reagents capable of identifying one or more unique nucleic acid or amino acid sequences, respectively. Preferably, a reagent distinguishes one member of the group comprising hcVβ3, hcVβ4, hcVβ12, hcVβ72, hcVβ21, hcVβ54 or hcVβ182 nucleic acid molecules or hcVβ3, hcVβ4, hcVβ12, hcVβ72, hcVβ21, hcVβ54 or hcVβ182 proteins, preferably $nCaV\beta3_{381}$, $nCaV\beta4_{408}$, $nCaV\beta12_{408}$, $nCaV\beta72_{438}$, $nCaV\beta21_{462}$, $nCaV\beta54_{417}$, $nCaV\beta182_{423}$, $PCaV\beta3_{127}$, $PCaV\beta4_{128}$, $PCaV\beta12_{134}$, $PCaV\beta72_{133}$, $PCaV\beta21_{130}$, $PCaV\beta54_{135}$ or $PCaV\beta182_{128}$, from another member of that group. By determining increased production of one of the detectable products, one can detect T cell expansion. Preferably, expansion of a T cell is determined by comparing formation of one detectable product with formation of one or more other detectable products and looking for increased production of at least one of the products compared to another. According to the present invention, a detectable product can comprise a nucleic acid molecule, a peptide, a protein or an antibody. Preferred detectable products and methods to form detectable products are disclosed herein. It is within the skill of one in the art that methods to identify detectable products based on the product being detected.

The invention also provides novel reagents useful in the methods which have been described herein above. Thus, the invention includes reagents capable of binding to unique nucleic acid or unique amino acid sequences contained within a TCR Vß. Preferred reagents include those which can differentiate one TCR V beta protein, or

nucleic acid molecule, from another. Preferred reagents can distinguish TCR V beta proteins hcVβ2, hcVβ3, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182, or the nucleic acid molecules that encode them, from each other. More preferred reagents can distinguish proteins comprising $PCaV\beta3_{127}$, $PCaV\beta3_{111}$, $PCaV\beta3_{110}$, $PCaV\beta4_{128}$, $PCaV\beta4_{113}$, $PCaV\beta4_{109}$, $PCaV\beta12_{134}$, $PCaV\beta12_{111}$, $PCaV\beta12_{115}$, $PCaV\beta72_{133}$, $PCaV\beta72_{113}$, $PCaV\beta72_{114}$, $PCaV\beta21_{130}$, $PCaV\beta21_{108}$, $PCaV\beta21_{116}$, $PCaV\beta54_{135}$, $PCaV\beta54_{114}$, $PCaV\beta54_{116}$, $PCaV\beta182_{128}$, $PCaV\beta182_{110}$ and/or $PCaV\beta182_{109}$ from each other, or nucleic acid molecules comprising $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$,$nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ and/or $nCaV\beta182_{327}$ from each other. Even more preferred reagents can distinguish TCR V beta proteins comprising amino acid sequence SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47 from each other.

In particular, a method of the present invention comprises: (a) contacting a sample, i.e., one or more samples, containing DNA from T cells with a reagent, i.e., one or more reagents, having specificity for a unique nucleic acid sequence; and (b) determining the presence of DNA carrying the unique nucleic acid sequences. Methods to determine the presence of the DNA are disclosed herein.

In one embodiment, identifying the presence of a T cell receptor having unique sequence can be achieved by polymerase chain reaction (PCR) amplification techniques known to those of skill in the art. The PCR amplification forms a detectable product comprising DNA. An example of a suitable reagent to use in PCR amplification techniques is a DNA primer complementary to all or a portion of a unique nucleic acid sequence, referred to herein as a unique sequence primer. Preferably, another primer is used in conjunction with the unique sequence primer in order o effect amplification. This second primer can be complementary to a unique sequence or to a common sequence (i.e., a sequence shared by different TCR beta chain sequences). Typically, the second primer is complementary to a common sequence and is chosen based on its distance from the unique sequence primer, i.e. based on ease of detection of PCR

amplification product. One of skill in the art understands that a preferred product of a PCR reaction is from about 100 to about 500 nucleotides, preferably from about 150 to about 450 nucleotides and more preferably from about 200 to about 400 nucleotides. Thus, it is within the skill of one in the art to design and create a second primer located from about 100 to about 500 nucleotides from the site of a unique sequence. For example, a suitable second primer includes a DNA primer complementary to a sequence in the constant region of a beta chain. Preferred second primers are described herein in the Examples section. Methods to resolve PCR products are well known to those of skill in the art. In addition, methods to quantitate the amount of PCR product produced in a PCR reaction are well known to those of skill in the art. Examples of preferred unique nucleic acid sequences to be identified by PCR include unique sequences contained within SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27 and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80. More preferred unique nucleic acid sequences to be identified by PCR include SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and/or SEQ ID NO:56, or complements thereof. Preferred second primers include primers located in the constant region sequence of a beta chain. More preferred second primers include SEQ ID NO:58 and SEQ ID NO:59, or complements thereof.

In another embodiment, identifying the presence of a T cell receptor having a unique nucleic acid sequence can be achieved by nucleic acid, e.g., DNA, RNA, modified DNA or modified RNA, hybridization techniques using a nucleic acid probe. The hybridization forms a detectable product comprising a hybrid between the nucleic acid and the reagent. A suitable reagent for use with hybridization techniques include nucleic acid probes which are complementary to nucleic acid sequences that include all

or a portion of a unique sequence. The hybridization forms a detectable product comprising a hybrid between the nucleic acid and the reagent. It is within the skill of one in the art to design and produce suitable probes based on sequences of the present invention. The presence of a unique sequence in a sample from an animal is determined by detecting the hybridization of a "unique sequence" probe to that unique sequence in the TCR Vβ nucleic acid molecule. Methods to detect hybridization of a probe are well known to those of skill in the art and include those that allow one to distinguish one Vβ nucleic acid from another. In addition, methods to quantitate the extent of hybridization are well known to those of skill in the art. Preferred unique nucleic acid sequences to be identified by nucleic acid hybridization include unique sequences contained within SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27 and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80. More preferred unique nucleic acid sequences to be identified by nucleic acid hybridization include unique sequences SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and/or SEQ ID NO:56.

A unique amino acid sequence of the present invention can be used to produce antibodies that bind specifically to the portion of a TCR Vß protein that contains the unique amino acid sequence. Such antibodies can be monoclonal or polyclonal, and produced using methods described herein. The antibodies can be used to detect T cells having T cell receptors containing such unique sequences by contacting T cells isolated from an animal with the antibody under appropriate conditions known in the art that enable formation of a complex between an antibody and a T cell receptor in a specific manner, i.e., such that the antibody only binds specifically a particular TCR Vß. The complex between an antibody and a T cell receptor is a detectable product. Methods to

detect such complex formation are known to those of skill in the art and include, for example, using a detectable moiety such as a radioisotope, an enzyme or a fluorescent dye, to detect complex formation. Preferred unique amino acid sequences to be identified using antibodies include antibodies that bind specifically to a unique amino acid sequence contained within SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80. Particularly preferred unique amino acid sequences to be identified using antibodies include antibodies that bind specifically to unique amino acid sequences encoded by a nucleic acid sequence SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56.

In another embodiment, identifying the presence of a T cell receptor having a unique nucleic acid sequence can be achieved by PCR amplification and nucleic acid sequencing techniques. Suitable reagents for use with such techniques include DNA primers which are complementary to common sequences (i.e., sequences shared by two or more TCR Vß molecules) that flank all or a portion of a unique sequence. It is within the skill of one in the art to design and produce suitable primers based on sequences of the present invention. The presence of a unique sequence in a sample from an animal is determined by sequencing the PCR product produced using the common sequence primers and identifying whether one or more nucleic acid sequences are present in the PCR product. An example of such method is described in Example 4 herein. Methods to produce and sequence PCR products are well known to those of skill in the art. T cell expansion is determined by identifying the heterogeneity or homogeneity of nucleic acid sequence displayed in a DNA fingerprint profile of a given sequence in a given sample of PCR products.

Preferred reagents include, but are not limited to, DNA primers or probes complementary to unique nucleic acid sequences contained in SEQ ID NO:1, SEQ ID

NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27 and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, including DNA primers or probes comprising SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56; or antibodies that bind specifically to an amino acid sequence encoded by a comprising SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and/or SEQ ID NO:56, or to other unique amino acid sequences in larger proteins.

One embodiment of the present invention is a method of detecting T cell expansion in an animal comprising detecting the expansion of a T cell receptor having a unique amino acid sequence within a protein selected from the group consisting of hcVβ3, hcVβ4, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182 proteins by forming detectable products, wherein the increased level of a detectable product compared with another detectable product indicates expansion of the T cells. Preferred Vβ proteins containing unique amino acid sequence include $PCaV\beta3_{127}$, $PCaV\beta3_{111}$, $PCaV\beta3_{110}$, $PCaV\beta4_{128}$, $PCaV\beta4_{113}$, $PCaV\beta4_{109}$, $PCaV\beta12_{134}$, $PCaV\beta12_{111}$, $PCaV\beta12_{115}$, $PCaV\beta72_{133}$, $PCaV\beta72_{113}$, $PCaV\beta72_{114}$, $PCaV\beta21_{130}$, $PCaV\beta21_{108}$, $PCaV\beta21_{116}$, $PCaV\beta54_{135}$, $PCaV\beta54_{114}$, $PCaV\beta54_{116}$, $PCaV\beta182_{128}$, $PCaV\beta182_{110}$ and/or $PCaV\beta182_{109}$.

Examples of samples useful a method of the present invention include samples from an animal that contains T cells. Preferably, a sample to be tested using a method of the present invention comprises blood, synovial fluid, lung lavage, saliva, spleen, thymus, tumors, granulomas, abscesses, edematous fluid, central nervous system fluid.

Preferred animals from which to isolate a sample of the present invention includes a mammal, more preferably a canid and more preferably a dog.

Any method of the present invention can be used to determine the disease state of an animal. Such methods can be used to determine the presence or absence of disease in an animal, including an animal susceptible to disease, an animal suspected of having disease, an animal having disease or an animal being or having been treated for a disease. Examples of specific diseases that can be diagnosed using a method of the present invention include: various forms of cancer, e.g., lymphoma and leukemia; various autoimmune diseases, e.g., rheumatoid arthritis or diabetes; various infectious diseases, such as those caused by viruses, by a yeast, e.g. of the genus Candida, by a parasite, e.g., Trichinella, Leishmania, Toxoplasma, a filariid, a mycobacterium, a protozoan, and by a bacterium; and allergies involving T cells, e.g. allergic dermatitis, atopic dermatitis, allergic bronchitis or allergic rhinitis.

A preferred embodiment of the present invention is a method to diagnose T cell cancer comprising: (a) contacting a sample containing DNA from an animal with a DNA primer that is complementary to a unique nucleic acid sequence within a nucleic acid molecule including $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$, $nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ or $nCaV\beta182_{327}$; and (b) diagnosing the cancer by determining the amount of DNA containing the unique nucleic acid sequence by comparing the amount so determined with the amount of DNA containing the unique sequence from a normal animal. According to the present invention, "a DNA primer" refers to one or more primers and "a unique nucleic acid sequence" refers to one or more unique nucleic acid sequences.

Another preferred embodiment of the present invention is a method to diagnose T cell cancer comprising: (a) contacting a sample containing DNA from an animal with a DNA primer that is complementary to a unique nucleic acid sequence within nucleic acid molecule selected from the group consisting of $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$,

$nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$,$nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ or $nCaV\beta182_{327}$; and (b) diagnosing cancer by quantitatively determining the ratio of DNA containing each of the unique nucleic acid sequences and by comparing the amount of DNA containing each of the unique sequence with each other.

The present invention also includes a kit comprising one or more reagents of the present invention. Preferred reagents include those which can differentiate TCR V beta proteins or nucleic acid molecules that encode such proteins. Preferred TCR V beta proteins include hcVβ2, hcVβ3, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182, with $PCaV\beta3_{127}$, $PCaV\beta3_{111}$, $PCaV\beta3_{110}$, $PCaV\beta4_{128}$, $PCaV\beta4_{113}$, $PCaV\beta4_{109}$, $PCaV\beta12_{134}$, $PCaV\beta12_{111}$, $PCaV\beta12_{115}$, $PCaV\beta72_{133}$, $PCaV\beta72_{113}$, $PCaV\beta72_{114}$, $PCaV\beta21_{130}$, $PCaV\beta21_{108}$, $PCaV\beta21_{116}$, $PCaV\beta54_{135}$, $PCaV\beta54_{114}$, $PCaV\beta54_{116}$, $PCaV\beta182_{128}$, $PCaV\beta182_{110}$ and/or $PCaV\beta182_{109}$ being more preferred and proteins comprising SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:20, SEQ ID NO:23, SEQ ID NO:26, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:41, SEQ ID NO:44, SEQ ID NO:47, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80 and/or proteins encoded by the complement of a nucleic acid sequence including SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56 being even more preferred. Preferred TCR V beta nucleic acid molecules include hcVβ2, hcVβ3, hcVβ12, hcVβ72, hcVβ21, dtb54 or dtb182, with $nCaV\beta3_{381}$, $nCaV\beta3_{333}$, $nCaV\beta3_{330}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta4_{351}$, $nCaV\beta4_{339}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta12_{339}$, $nCaV\beta12_{345}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta72_{423}$, $nCaV\beta72_{342}$, $nCaV\beta21_{462}$, $nCaV\beta21_{390}$, $nCaV\beta21_{396}$, $nCaV\beta21_{348}$, $nCaV\beta54_{417}$, $nCaV\beta54_{405}$,$nCaV\beta54_{354}$, $nCaV\beta54_{348}$, $nCaV\beta182_{423}$, $nCaV\beta182_{384}$, $nCaV\beta182_{369}$ and/or $nCaV\beta182_{327}$ being more preferred and nucleic acid molecules comprising sequences SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ

ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27,SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, a complement of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and/or a nucleic acid molecule that encodes a protein having an amino acid sequence including SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 or SEQ ID NO:80, and complements thereof, being even more preferred. A kit of the present invention can include mixtures of reagents disclosed herein.

The following examples are provided for the purposes of illustration and are not intended to limit the scope of the present invention.

EXAMPLES

It is to be noted that the examples include a number of molecular biology, microbiology, immunology and biochemistry techniques considered to be familiar to those skilled in the art. Disclosure of such techniques can be found, for example, in Sambrook et al., *ibid.* and Ausubel, et al., 1993, *Current Protocols in Molecular Biology*, Greene/Wiley Interscience, New York, NY, and related references. It should also be noted that since nucleic acid sequencing technology, and in particular the sequencing of PCR products, is not entirely error-free, that the nucleic acid and deduced protein sequences presented herein represent apparent nucleic acid sequences of the nucleic acid molecules encoding TCR Vβ proteins of the present invention.

Example 1

This example describes the isolation and sequencing of canine T cell receptor (TCR) Vβ nucleic acid molecules.

Canine TCR Vβ nucleic acid molecules were produced as follows. RNA was purified from mitogen activated canine peripheral blood lymphocytes and resuspended in water at about 2.5 X 10^5 cell equivalent/microliter (μl). About 5 μl of RNA and random hexanucleotide primers were used to synthesize cDNA using the First Strand cDNA Synthesis™ kit (available from Pharmacia, Uppsala, Sweden). TCR Vβ genes were selectively PCR amplified from the cDNA using degenerate oligonucleotides designed using the conserved sequence motifs WYRQ and Y(Y/F)CA of T and B cell antigen receptors (Rast and Litman, *Proc. Natl. Acad. Sci. USA*, vol. 91, p. 9248, 1994). The degenerate primer FR2, having the nucleic acid sequence 5' CCG AAT TCT GGT A(TC) C(GA) NCA 3' (SEQ ID NO:81) was used in combination with either the FR3A primer, having the nucleic acid sequence 5' CGG ATC CGC (GA)CA (GA)TA (GA)T A 3' (SEQ ID NO:82) or the primer FR3B, having the nucleic acid sequence 5' CGG ATC CGC (GA)CA (GA)A A(GA)T A 3' (SEQ ID NO:83). First round PCR reactions were performed in about 50μl of 50 mM KCl, 10 mM Tris-HCl, 0.01% gelatin (pH 8.3), 3.5 mM $MgCl_2$, 0.2 mM of each of the four deoxyribonucleotide triphosphates (dNTP), about 1μM of each primer and about 2.0 units Taq polymerase (available from Perkin-Elmer). This reaction mixture was created after attempts using published methods failed. Moreover, 20 additional cycles of PCR using about 5μl of the first round PCR sample as template under identical conditions were needed to obtain useful second round PCR product. No PCR products were identified after 30 cycles. Second round PCR products were resolved by loading about 15 μl of the second round PCR product onto a 1.0% agarose gel in TBE buffer and staining the gel with ethidium bromide.

No PCR product was obtained using the FR2 primer combined with the FR3A primer. Several bands of DNA were obtained using the FR2 primer combined with the FR3B primer, one of which migrated at a predicted size of about 190 base pair (bp). This band was excised, and the DNA was purified using Qiaquick gel extraction kit (available from Qiagen, Chatsworth, CA) according to the manufacturer's instructions. The purified DNA was cloned into the pCR 2.1 vector (available from Invitrogen, San Diego, CA), and used to transform DH5α *E. coli* cells (available from Invitrogen). The transformed colonies were grown overnight in about 2 ml LB media containing about 100 μg/ml ampicillin. Plasmid DNA was purified using BioRad's Quantum Prep™

mini-prep kit (available from BioRad, Hercules, CA). Inserted sequence in 11 different plasmid samples were subjected to DNA sequence analysis using standard sequencing methods. Three different nucleic acid sequences were obtained. The 3 different nucleic acid molecules are referred to herein as hcvb3, hcvb4 and hcvb12.

The sequences obtained above indicated that incomplete nucleic acid molecules were obtained using the foregoing PCR procedure. To obtain more complete clones of the PCR products, primers were designed using the nucleic acid sequences obtained above, including primer Phcvb3, having the nucleic acid sequence 5' CCA GAC CTG GGT CTT GTC G 3' (SEQ ID NO:84), primer Phcvb4, having the nucleic acid sequence 5' CTC TGT CCT GGG AGC TGA C 3' (SEQ ID NO:85), and primer Phcvb12, having the nucleic acid sequence 5' TTG TTT GAT CTA GAG ACT GTG 3' (SEQ ID NO:86). Each primer was then used in combination with the 5' vector primer T3 (available from available from Stratagene Cloning Systems, La Jolla, CA) to amplify PCR products representing Vβ genes from a canine PBL cDNA library generated in the λ Zap II vector (available from Stratagene Cloning Systems, La Jolla, CA). The *C. familiaris* mitogen activated PBMC cDNA library was constructed in the Uni-ZAP® XR vector (available from Stratagene Cloning Systems), using Stratagene's ZAP-cDNA® Synthesis Kit and the manufacturer's protocol. The mRNA was isolated from *C. familiaris* peripheral blood mononuclear cells 4 hours after they were activated by a polyclonal activating agent in culture. PCR reaction were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min, about 94°C for about 30 sec., about 58°C for about 30 sec., and about 72°C for about 1 min. for about 35 cycles, then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 25 mM $MgCl_2$, about 1 unit Amplitaq Gold™ (available from Perkin-Elmer Cetus), about 200 μM dNTP's and about 1 μM primer.

The resulting PCR products were gel purified, cloned and sequenced using standard methods. The resulting nucleic acid sequences were aligned with the nucleic acid sequences obtained from the first set of PCR products to obtain a more complete sequence of hcvb3, hcvb4 and hcvb12. Since the PCR primers used to generate the first set of PCR products were degenerate primers, the nucleic acid sequences of hcvb3,

hcvb4 and hcvb12 at the degenerate primer sites were ambiguous. To determine the sequence in the area of the degenerate primers, PCR primers corresponding to the newly derived extreme 5' ends of the hcvb3, hcvb4 and hcvb12 nucleic acid molecules were designed. Primer 5'Phcvb3, having the nucleic acid sequence 5' ATC GGA CTC CTC TGT GGT GT 3' (SEQ ID NO:87), primer 5'hcvb4, having the nucleic acid sequence 5' ACG GTG AAG GGC TAG CAC CT 3' (SEQ ID NO:88) and primer 5'hcvb12, having the nucleic acid sequence 5' GCT GAA ATG GCC ACC GGC GT 3' (SEQ ID NO:89), each were used in combination with a primer specific for a sequence in the constant region of a TCR beta chain (SED ID NO:57) in PCR reactions using the cDNA library described above. The resulting PCR products were purified, cloned into PCR2.1 vector (available from Invitrogen)and sequenced using standard methods.

A. A first clone (hcVβ3) was isolated, referred to herein as $nCaV\beta3_{381}$, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:1. SEQ ID NO:1 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:1 is represented herein by SEQ ID NO:3. Translation of SEQ ID NO:1 suggests that nucleic acid molecule $nCaV\beta3_{381}$ encodes a TCR Vβ protein of about 127 amino acids, denoted herein as $PCaV\beta3_{127}$, the amino acid sequence of which is presented in SEQ ID NO:2, assuming an open reading frame having a first codon spanning from nucleotide 1 through nucleotide 3 of SEQ ID NO:1 and a last codon spanning from nucleotide 379 through nucleotide 381 of SEQ ID NO:1. The putative signal sequence extends from nucleotide 1 to nucleotide 51 of SEQ ID NO:1. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta3_{110}$, contains about 110 amino acids, extending from residue 18 through residue 127 of SEQ ID NO:2. The nucleic acid molecule encoding $PCaV\beta3_{110}$ is denoted herein as $nCaV\beta3_{330}$, extending from nucleotide 52 through nucleotide 381 of SEQ ID NO:1.

Comparison of nucleic acid sequence SEQ ID NO:1 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:1 showed the most homology, i.e., about 69% identity, between SEQ ID NO:1 and a human TCR β chain gene (Genbank Accession No. Z223040). Comparison of amino acid sequence SEQ ID NO:2 with amino acid sequences reported in GenBank indicates that SEQ ID NO:2 showed the

most homology, i.e., about 65% identity, between SEQ ID NO:2 and an *Ovis aries* TCR Vβ chain protein (Genbank Accession No. gi 2665554).

B. A second clone (hcVβ4) was isolated, referred to herein as $nCaV\beta4_{408}$, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:4. SEQ ID NO:4 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:4 is represented herein by SEQ ID NO:6. Translation of SEQ ID NO:4 suggests that nucleic acid molecule $nCaV\beta4_{408}$ encodes a TCR Vβ protein of about 128 amino acids, denoted herein as $PCaV\beta4_{128}$, the amino acid sequence of which is presented in SEQ ID NO:5, assuming an open reading frame having an initiation codon spanning from nucleotide 24 through nucleotide 26 of SEQ ID NO:4 and a last codon spanning from nucleotide 405 through nucleotide 407 of SEQ ID NO:4. The coding region encoding $PCaV\beta4_{128}$ is presented herein as $nCaV\beta4_{384}$, which has the nucleotide sequence SEQ ID NO:6 (the coding strand) and SEQ ID NO:7 (the complementary strand). The putative signal sequence extends from nucleotide 25 to nucleotide 69 of SEQ ID NO:4. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta4_{113}$, contains about 113 amino acids, extending from residue 60 through residue 128 of SEQ ID NO:5. The nucleic acid molecule encoding $PCaV\beta4_{113}$ is denoted herein as $nCaV\beta4_{339}$, extending from nucleotide 70 through nucleotide 408 of SEQ ID NO:4.

Comparison of nucleic acid sequence SEQ ID NO:4 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:4 showed the most homology, i.e., about 75% identity, between SEQ ID NO:4 and a human TCR β chain gene (Genbank Accession No. M97713). Comparison of amino acid sequence SEQ ID NO:5 with amino acid sequences reported in GenBank indicates that SEQ ID NO:5 showed the most homology, i.e., about 69% identity, between SEQ ID NO:5 and an *Ovis aries* TCR Vβ chain protein (Genbank Accession No. gi 2665558).

C. A third clone (hcVβ12) was isolated, referred to herein as $nCaV\beta12_{408}$, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:9. SEQ ID NO:9 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:9 is represented herein by SEQ ID NO:11. Translation of SEQ ID NO:9 suggests that nucleic acid molecule $nCaV\beta12_{408}$ encodes a

TCR Vβ protein of about 134 amino acids, denoted herein as $PCaV\beta12_{134}$, the amino acid sequence of which is presented in SEQ ID NO:10, assuming an open reading frame having an initiation codon spanning from nucleotide 7 through nucleotide 9 of SEQ ID NO:9 and a last codon spanning from nucleotide 406 through nucleotide 408 of SEQ ID NO:9. The coding region encoding $PCaV\beta12_{134}$ is presented herein as $nCaV\beta12_{402}$, which has the nucleotide sequence SEQ ID NO:12 (the coding strand) and SEQ ID NO:13 (the complementary strand). The putative signal sequence extends from nucleotide 7 to nucleotide 63 of SEQ ID NO:9. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta12_{115}$, contains about 115 amino acids, extending from residue 20 through residue 134 of SEQ ID NO:10. The nucleic acid molecule encoding $PCaV\beta12_{115}$ is denoted herein as $nCaV\beta12_{345}$, extending from nucleotide 64 through nucleotide 408 of SEQ ID NO:9.

Comparison of nucleic acid sequence SEQ ID NO:9 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:9 showed the most homology, i.e., about 72% identity, between SEQ ID NO:9 and a *Macaca mulatta* TCR β chain mRNA (Genbank Accession No. U04578). Comparison of amino acid sequence SEQ ID NO:10 with amino acid sequences reported in GenBank indicates that SEQ ID NO:10 showed the most homology, i.e., about 57% identity, between SEQ ID NO:10 and a human TCR Vβ protein (Genbank Accession No. I38312).

Example 2

This example describes the isolation and sequencing of two additional canine TCR Vβ nucleic acid molecules.

Two canine TCR Vβ nucleic acid molecules were PCR amplified from the canine PBL cDNA library described above in Example 1. A pair of primers was used to amplify DNA from the cDNA library. The 5' vector primer T3, described in Example 1, was used in combination with primer Phcvb21, having the nucleic acid sequence 5' CTG TTG CCC ACG TTA GAG G 3' (SEQ ID NO:90) or primer Phcvb72, having the nucleic acid sequence 5' TTA CTG AAC TGC TGC ACT G 3' (SEQ ID NO:91). PCR reaction were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30

sec., about 72°C for about 1 min. for about 35 cycles; then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM $MgCl_2$, about 1 unit Amplitaq Gold, about 200 μM dNTP's and about 1 μM primer. The resultant PCR products obtained using standard PCR conditions (e.g., Sambrook et al., *ibid.*), were gel purified, cloned and sequenced. The PCR products are referred to herein as hcvb21 or hcvb72, respectively.

The sequences obtained were compared with sequences disclosed in Ito et al., *Immunogenetics*, vol. 38, p. 60, 1993 or Takano et al., *Immunogenetics*, vol. 40, p. 246, 1994. The PCR products hcvb21 or hcvb72 were found to contain more 5' nucleic acid sequence than that disclosed in the above-referenced publications. To obtain more complete nucleic acid molecules containing the V, D and J regions, PCR amplification was performed using primers designed from the 5' sequence obtained from hcvb21 or hcvb72 nucleic acid molecules. Primer 5'Phcvb21, having the nucleic acid sequence 5' GCT GCA GGA TTC GGC ACG AG 3' (SEQ ID NO:92) or primer 5'Phcvb72, having the nucleic acid sequence 5' TAC GAC TGT CAG CTT GGT CC 3' (SEQ ID NO:93), each were used in conjunction with a TCR beta constant region primer (SEQ ID NO:57) to amplify these sequences from mRNA prepared from canine concavalin A (ConA) activated PBMC. The PCR products were cloned and sequenced using standard methods.

A. The clone hcVβ21 was isolated, referred to herein as $nCaV\beta21_{462}$, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:19. SEQ ID NO:19 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:19 is represented herein by SEQ ID NO:21. Translation of SEQ ID NO:19 suggests that nucleic acid molecule $nCaV\beta21_{462}$ encodes a TCR Vβ protein of about 130 amino acids, denoted herein as $PCaV\beta21_{130}$, the amino acid sequence of which is presented in SEQ ID NO:20, assuming an open reading frame having an initiation codon spanning from nucleotide 73 through nucleotide 75 of SEQ ID NO:19 and a last codon spanning from nucleotide 460 through nucleotide 462 of SEQ ID NO:19. The coding region encoding $PCaV\beta21_{130}$ is presented herein as $nCaV\beta21_{390}$, which extends from nucleotide 73 to nucleotide 462 of SEQ ID NO:19.

The putative signal sequence extends from nucleotide 73 to nucleotide 114 of SEQ ID NO:19. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta21_{116}$, contains about 116 amino acids, extending from residue 15 through residue 130 of SEQ ID NO:19. The nucleic acid molecule encoding $PCaV\beta21_{116}$ is denoted herein as $nCaV\beta21_{348}$, extending from nucleotide 115 through nucleotide 462 of SEQ ID NO:19.

A comparison of SEQ ID NO:19 with the DNA sequence DTCRB21 described in Ito et al., *ibid.* indicated that SEQ ID NO:19 is 221 nucleotides longer than at the 5'end of DTCRB21. The sequences of SEQ ID NO:19 and DTCR21 overlap by 176 nucleotides with 100% identity, corresponding to nucleotides 222 through 398 of SEQ ID NO:19. An alignment of SEQ ID NO:19 with DTCR21 is shown in Table 1.

TABLE 1. Nucleotide Sequence Comparison of hcvb21 and DTCRB21

```
DTCRB21          ---------- ---------- ---------- ---------- ----------
SEQ ID NO:19     GCTGCAGGAT TCGGCACGAG GCGTGGTCAT ATCTATCTTG AGAGAGGTAT

DTCRB21          ---------- ---------- ---------- ---------- ----------
SEQ ID NO:19     GGTATGAGGC CATCACCTGA AGATGCTGAT GCTTCTGCTG CTCCTGGGGC

DTCRB21          ---------- ---------- ---------- ---------- ----------
SEQ ID NO:19     CCAGCTCTGG ACTCGGTGCC CTCGTCTTCC AGGCGCCCAG CACAATGATC

DTCRB21          ---------- ---------- ---------- ---------- ----------
SEQ ID NO:19     TGTAAGAGCG GAGCCACCGT GCAGATCCAG TGTCAAACAG TGGACCTTCA

DTCRB21          ---------- ---------- -TCGCCAGCT CCCGAAGCAG GGCCTTACCC
SEQ ID NO:19     AGCCACAACC GTGTTTTGGT ATCGCCAGCT CCCGAAGCAG GGCCTTACCC

DTCRB21          TTATGGTGAC CTCTAACGTG GGCAACAGTG CTACACACGA GCAGGGGTTC
SEQ ID NO:19     TTATGGTGAC CTCTAACGTG GGCAACAGTG CTACACACGA GCAGGGGTTC

DTCRB21          CCTGCAGCCA AGTTCCCTGT TAACCACCCA AACCTCACGT TTTCCTCCCT
SEQ ID NO:19     CCTGCAGCCA AGTTCCCTGT TAACCACCCA AACCTCACGT TTTCCTCCCT

DTCRB21          GATGGTGACG AGTTCAGGTC CTGGAGACAG CGGCCTCTAC TTCTGTGGCT
SEQ ID NO:19     GATGGTGACG AGTTCAGGTC CTGGAGACAG CGGCCTCTAC TTCTGTGGTG

DTCRB21          ACC...TACA GGGCGCGCGC TACGAGCAGT ATTTCGGCGC CGGCACCAGG
SEQ ID NO:19     TTCGGGCGTA TGGTGGGAAC TCGCCCCTCT ACTTTGGAAC AGGCACCAGG

DTCRB21          CTCACGGTCC TC
SEQ ID NO:19     CTCACCGTGA CA
```

The amino acid sequence SEQ ID NO:20 is 50 amino acids longer at the 5'end than the amino acid sequence encoded by DTCR21. An alignment of SEQ ID NO:20 with the amino acid sequence encoded by DTCR21 is shown in Table 2.

TABLE 2. Amino Acid Sequence Comparison of hcvb21 and DTCR21.

```
SEQ ID NO:20  MLMLLLLLGP SSGLGALVFQ APSTMICKSG ATVQIQCQTV DLQATTVFWY
DTCRB21       ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~

SEQ ID NO:20  RQLPKQGLTL MVTSNVGNSA THEQGFPAAK FPVNHPNLTF SSLMVTSSGP
DTCRB21       RQLPKQGLTL MVTSNVGNSA THEQGFPAAK FPVNHPNLTF SSLMVTSSGP

SEQ ID NO:20  GDSGLYFCGV RAYGGNSPLY FGTGTRLTVT
DTCRB21       GDSGLYFCGY .LQGARYEQY FGAGTRLTVL
```

The amino acid sequence SEQ ID NO:20 is 50 amino acids longer at the 5'end than the amino acid sequence encoded by DTCR21. An alignment of SEQ ID NO:20 with the amino acid sequence encoded by DTCR21 is shown in Table 2.

Comparison of nucleic acid sequence SEQ ID NO:19 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:19 showed the most homology, i.e., about 38% identity, between SEQ ID NO:19 and a dog TCR β chain gene (Genbank Accession No. M97510). Comparison of amino acid sequence SEQ ID NO:20 with amino acid sequences reported in GenBank indicates that SEQ ID NO:20 showed the most homology, i.e., about 60% identity, between SEQ ID NO:20 and DTCR21 protein.

B. The clone hcVβ72 was isolated, referred to herein as $nCaV\beta72_{438}$, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:98. SEQ ID NO:98 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:98 is represented herein by SEQ ID NO:100. Translation of SEQ ID NO:98 suggests that nucleic acid molecule $nCaV\beta72_{438}$ encodes a TCR Vβ protein of about 133 amino acids, denoted herein as $PCaV\beta72_{133}$, the amino acid sequence of which is presented in SEQ ID NO:15, assuming an open reading frame having an initiation codon spanning from nucleotide 40 through nucleotide 42 of SEQ ID NO:98 and a last codon spanning from nucleotide 436 through nucleotide 438 of SEQ ID NO:98. The coding region encoding $PCaV\beta72_{133}$ is presented herein as $nCaV\beta72_{399}$, which has the nucleotide sequence SEQ ID NO:17 (the coding strand) and

SEQ ID NO:18 (the complementary strand). The putative signal sequence extends from nucleotide 40 to nucleotide 96 of SEQ ID NO:98. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta72_{114}$, contains about 114 amino acids, extending from residue 20 through residue 133 of SEQ ID NO:15. The nucleic acid molecule encoding $PCaV\beta72_{114}$ is denoted herein as $nCaV\beta72_{342}$, extending from nucleotide 142 through nucleotide 438 of SEQ ID NO:19.

A comparison of SEQ ID NO:98 with the DNA sequence DTB72 described in Takano et al., *ibid.* indicated that SEQ ID NO:98 differs substantially from the published canine TCR Vβ sequence. A comparison between SEQ ID NO:98 and DTB72 is shown in Table 3.

TABLE 3. Nucleotide Sequence Comparison of hcvb72 and DTB72

```
                                                                    ~~~~~
DTB72                                                               CACGA
SEQ ID NO:98

DTB72           ~~~~~~~~~~ ~~~~~~CAGC TTCCCAGGGC TGCCATGGGC TCCAGGCTTC
SEQ ID NO:98    GGAGCGGGGA GGCTATCAGC TTCCCAGGGC TGCCATGGGC TCCAGGCTTC

DTB72           TCTGCTGTGT GGCCCTTTTC TCCTGGGAGC CGGCCCCCGT GGAGTCTGAG
SEQ ID NO:98    TCTGCTGTGT GGCCCTTTGT CTCCTGGGAG CCGGCCCCGT GGAGTCTGAG

DTB72           GTCATCCAAA CTCCAAGACA CATGATCAAA GTCAAGAGGA CAGACAGTGA
SEQ ID NO:98    GTCATCCAAA CTCCAAGACA CATGATCAAA G.CAAGAGGA CAGACAGTGA

DTB72           CC...TGAGA TGTCCTTATC TCTGGACA.C TATCTGTGTA CTGGTACCAA
SEQ ID NO:98    CCCTGAGATG TTCCCTTATC TCTGGACACC TATCTGTGTA CTGGTACCAA

DTB72           CAGGCCTTGA TGGTCCGTTT ACCGGTTTCT CATTCAGT.. .........C
SEQ ID NO:98    CAGGCCCTG. GGCCAGGGTC CCCGGTTTCT CATTCAGTAT TACAATAGGG

DTB72           ATCATAGTCA AAAAAGAAAC ATCCGGTCAA GATTCTCAGT GCAGCAGTTC
SEQ ID NO:98    AAGAGAGAGA CAAAGGAGAC ATCCCGGCAA GATTCTCAGT GCAGCAGTTC

DTB72           AGTAACTACA GCATCCCAGC TTGAGATGAA CTCCCTGGAG CCAGGAGACT
SEQ ID NO:98    AGTAACTACA GC.TCCCAGC TGGAGATGAA CTCCCTGGAG CCAGGAGACT

DTB72           CAGCCCTATA TCTCTGTGCC AGCAGC...G GGTACAGTGA GAGCTACGAG
SEQ ID NO:98    CAGCCCTATA TCTCTGTGCC AGCAGCTTAG ATGCGTTCGA CGCGGGGCAG

DTB72           CGGTATTTCG GAGCCGGCAC CAGGCTCACG GTCCTC
SEQ ID NO:98    CTGTACTTCG GGGCCGGTTC CAAGCTGGCC GTGCTG
```

Comparison of SEQ ID NO:98 with DTB72 indicates that the identity between the two sequences is about 90%, when determined using the Compare function by maximum matching within the program DNAsis™ Version 2.1. A comparison of the amino acid

sequence SEQ ID NO:15 and the amino acid sequence encoded by DTB72 indicates that the identity between the two sequences is only 57%, when determined using the Compare function by maximum matching within the program DNAsis™ Version 2.1. An alignment of the two sequences is shown in Table 4.

TABLE 4. Amino Acid Sequence Comparison of hcvb72 and DTB72

```
SEQ ID NO:15   MGSRLLCCVA LCLLGAGPVE SEVIQTPRHM IKARGQTVTL RCSLISGHLS
DTB72          MGSRLLCCVA LFSWEPAPVE SEVIQTPRHM IKVKRTDSDL RCPYL.WTLS

SEQ ID NO:15   VYWYQQAL.G QGPRFLIQYY NREERDKGDI PARFSVQQFS NYSSQLEMNS
DTB72          VYWYQQALMV RLPVSHSVII VKKETSGQDS QCSSSV.... TTASQLEMNS

SEQ ID NO:15   LEPGDSALYL CASSLDAFDA GQLYFGAGSK LAVL
DTB72          LEPGDSALYL CASS.GYSES YERYFGAGTR LTVL
```

The comparison of the two sequences indicates that SEQ ID NO:98 and DTB72 encode different proteins.

Comparison of nucleic acid sequence SEQ ID NO:19 with nucleic acid sequences reported in GenBank indicates that SEQ ID NO:19 showed the most homology, i.e., about 60% identity, between SEQ ID NO:19 and a feline leukemia virus transduced TCR β chain gene (Genbank Accession No. X05155). Comparison of amino acid sequence SEQ ID NO:20 with amino acid sequences reported in GenBank indicates that SEQ ID NO:20 showed the most homology, i.e., about 65% identity, between SEQ ID NO:20 and a a feline leukemia virus transduced TCR β chain protein (Genbank Accession No. RWMVTV).

Example 3

This example describes the production of two canine TCR Vβ nucleic acid molecules.

Two canine TCR Vβ nucleic acid molecules were PCR amplified from the canine PBL cDNA library described above in Example 1. A pair of primers was used to amplify DNA from the cDNA library. The 5' vector primer T3, described in Example 1, was used in combination with primer Pdtb54, having the nucleic acid sequence 5' CTT TTG CTG GGA TCT GCT GA 3' (SEQ ID NO:94) or primer Pdtb182, having the nucleic acid sequence 5' CAG TTG CTT AG GTC TTG CT 3' (SEQ ID NO:95). The resultant PCR products obtained using standard PCR conditions (e.g., Sambrook et al.,

ibid.), were gel purified, cloned and sequenced. The PCR products are referred to herein as dtb54 or dtb182, respectively.

The sequences obtained were compared with sequences disclosed in Takano et al., *ibid.* The PCR products dtb54 or dtb182 were found to contain more 5' nucleic acid sequence than that disclosed in the above-referenced publication. To obtain more complete nucleic acid molecules containing the V, D and J regions, PCR amplification was performed using primers designed from the 5' sequence obtained from dtb54 or dtb182 nucleic acid molecules. Primer 5'Pdtb54, having the nucleic acid sequence 5' CAC GAG CCT GCC ATG TGC CC 3' (SEQ ID NO:96) or primer 5'Pdtb182, having the nucleic acid sequence 5' GGC ACG AGC ACT GAG GAC CA 3' (SEQ ID NO:97), each were used in conjunction with a TCR beta constant region primer (SEQ ID NO:57) to amplify these sequences from mRNA prepared from canine concavalin A (ConA) activated PBMC. The PCR products were cloned and sequenced using standard methods.

A. The clone dtb54 was isolated, referred to herein as $nCaV\beta54_{417}$, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:22. SEQ ID NO:22 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:22 is represented herein by SEQ ID NO:24. Translation of SEQ ID NO:22 suggests that nucleic acid molecule $nCaV\beta54_{417}$ encodes a TCR Vβ protein of about 135 amino acids, denoted herein as $PCaV\beta54_{135}$, the amino acid sequence of which is presented in SEQ ID NO:23, assuming an open reading frame having an initiation codon spanning from nucleotide 13 through nucleotide 15 of SEQ ID NO:22 and a last codon spanning from nucleotide 415 through nucleotide 417 of SEQ ID NO:22. The coding region encoding $PCaV\beta54_{135}$ is presented herein as $nCaV\beta54_{405}$, which extends from nucleotide 13 to nucleotide 417 of SEQ ID NO:22. The putative signal sequence extends from nucleotide 13 to nucleotide 69 of SEQ ID NO:22. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta54_{116}$, contains about 116 amino acids, extending from residue 20 through residue 135 of SEQ ID NO:22. The nucleic acid molecule encoding $PCaV\beta54_{116}$ is denoted herein as $nCaV\beta54_{348}$, extending from nucleotide 70 through nucleotide 417 of SEQ ID NO:22.

A comparison of SEQ ID NO:22 with the DNA sequence DTB54 described in Takano et al., *ibid.* indicated that the sequences are substantially similar except for 12 additional nucleotides at the 5'end and an additional amino acid at residue 55 in SEQ ID NO:22.

B. The clone dtb182 was isolated, referred to herein as $nCaV\beta182_{423}$, the coding strand of which was shown to have a nucleic acid sequence denoted herein as SEQ ID NO:25. SEQ ID NO:25 includes the V, D and J regions of the sequenced PCR product. The complement of SEQ ID NO:25 is represented herein by SEQ ID NO:27. Translation of SEQ ID NO:25 suggests that nucleic acid molecule $nCaV\beta182_{423}$ encodes a TCR Vβ protein of about 128 amino acids, denoted herein as $PCaV\beta182_{128}$, the amino acid sequence of which is presented in SEQ ID NO:26, assuming an open reading frame having an initiation codon spanning from nucleotide 40 through nucleotide 43 of SEQ ID NO:25 and a last codon spanning from nucleotide 421 through nucleotide 423 of SEQ ID NO:25. The coding region encoding $PCaV\beta182_{128}$ is presented herein as $nCaV\beta182_{384}$, which extends from nucleotide 40 to nucleotide 423 of SEQ ID NO:25. The putative signal sequence extends from nucleotide 40 to nucleotide 96 of SEQ ID NO:25. The proposed mature protein (i.e., canine TCR Vβ protein from which the signal sequence has been cleaved), denoted herein as $PCaV\beta182_{109}$, contains about 109 amino acids, extending from residue 20 through residue 128 of SEQ ID NO:25. The nucleic acid molecule encoding $PCaV\beta182_{109}$ is denoted herein as $nCaV\beta182_{327}$, extending from nucleotide 97 through nucleotide 423 of SEQ ID NO:25.

A comparison of SEQ ID NO:25 with the DNA sequence DTB182 described in Takano et al., *ibid.* indicated that the sequences are substantially similar except for 84 additional nucleotides at the 5'end of SEQ ID NO:25.

Example 4

This example describes the identification of unique TCR Vβ sequences by designing PCR primers that distinguish between different (TCR) Vβ nucleic acid molecules.

Seven different primers for PCR reactions were designed to amplify DNA from seven different TCR Vβ nucleic acid molecules. The primers were designed based on

the nucleic acid sequences SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:9, SEQ ID NO:98, SEQ ID NO:19, SEQ ID NO:22 or SEQ ID NO:25. The inventors discovered unique sequences for each of the foregoing nucleic acid molecules that are not shared between each of the different molecules. In addition, the inventors discovered which primers designed based on those unique sequences, and under what specific conditions, did not cross-prime between the different nucleic acid molecules. For some Vβ genes, several different Vβ primers to unique sequences had to be tested in order to find one that was specific to only one Vβ gene. Some of the primers that were designed include: primer hcVβ3 unique, having the nucleic acid sequence 5' CGA CAA GAC CCA GGT CTG G 3' (SEQ ID NO:50), complementary to nucleotides 157 to 175 of SEQ ID NO:1; primer hcVβ4 unique, having the nucleic acid sequence 5' GTC AGC TCC CAG GAC AGA G
3' (SEQ ID NO:51), complementary to nucleotides 176 to 194 of SEQ ID NO:4; primer hcVβ12 unique, having the nucleic acid sequence 5' CAT GAC CTG GGA CAT GGG C 3' (SEQ ID NO:52), complementary to nucleotides 172 to 190 of SEQ ID NO:9; primer hcVβ72 unique, having the nucleic acid sequence 5' GAG ATG TTC CCT TAT CT CTGG 3' (SEQ ID NO:53), complementary to nucleotides 201 to 226 of SEQ ID NO:98; primer hcVβ21 unique, having the nucleic acid sequence 5' CCT CTA ACG TGG GCA ACA G 3' (SEQ ID NO:54), complementary to nucleotides 260 to 278 of SEQ ID NO:19; primer dtb54 unique, having the nucleic acid sequence 5' TCA GCA GAT CCC AGC AAA AG 3' (SEQ ID NO:55), complementary to nucleotides 174 to 193 of SEQ ID NO:22; and primer dtb182 unique, having the nucleic acid sequence 5' AGC AAG ACC TCA AGC AAC TG 3' (SEQ ID NO:56), complementary to nucleotides 203 to 222 of SEQ ID NO:25.

The ability of each primer to specifically prime a specific TCR Vβ gene was tested by performing PCR reactions using each of the above primers in combination with a Vβ constant region primer including: primer Cβ1, having the nucleic acid sequence 5' GTG ACC TTC TGC AGA TCC TC 3' (SEQ ID NO:57); primer Cβ2, having the nucleic acid sequence 5' AGC TCA GCT CCA CGT GGT C 3' (SEQ ID

NO:58); or primer Cβ3, having the nucleic acid sequence 5' TGC TGA ACC CAC TCG TGA C 3' (SEQ ID NO:59).

The specificity of these primers was first tested using 7 different DNA plasmids that contained nucleic acid molecules comprising either SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:9, SEQ ID NO:98, SEQ ID NO:19, SEQ ID NO:22 or SEQ ID NO:25 as templates for different PCR reaction. Each unique Vβ primer was used to amplify DNA from each template. PCR reactions were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30 sec., about 72°C for about 1 min. for about 35 cycles; then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM $MgCl_2$, about 1 unit Amplitaq Gold, about 0.1 μM dNTP's and about 0.4 μM primer. The results indicated that PCR products were only present when the correct template and primer combination was used. As such, only PCR products were present when primer hcVβ3 unique was used with a plasmid containing SEQ ID NO:1, primer hcVβ4 unique was used with a plasmid containing SEQ ID NO:4, primer hcVβ12 unique was used with a plasmid containing SEQ ID NO:9, primer hcVβ72 unique was used with a plasmid containing SEQ ID NO:98, primer hcVβ21 unique was used with a plasmid containing SEQ ID NO:19, primer dtb54 unique was used with a plasmid containing SEQ ID NO:22 or primer dtb182 unique was used with a plasmid containing SEQ ID NO:25.

The ability of the Vβ unique primers to prime DNA of the predicted size for different Vβ genes using cDNA from a canine ConA activated T cell population as template material was tested. The same primers and PCR amplification conditions described immediately above were used in these experiments. The resulting PCR products were resolved by electrophoresis on an about 1.2% LE agarose gel in TBE buffer and stained with ethidium bromide. The results shown in Fig. 1A indicated that all seven Vβ unique primers were able to prime DNA fragments of the correct size. To confirm that only a specific Vβ gene was amplified by each Vβ primer, the DNA bands shown in Fig. 1A were extracted from the gel and cloned. Different clones containing

DNA from the different bands were sequenced. The sequencing results indicated that each Vβ unique primer correctly primed only one Vβ gene containing sequence complementary to that primer.

Example 5

This example describes a method for identifying T cell expansion.

About 10^5 lymph node cells or PBMC were isolated from 2 dogs known to have lymphoma (Haynes and Stoll) and a control dog. cDNA samples from the cells were used as templates in separate PCR reactions using primer hcVβ3 unique, primer hcVβ4 unique, primer hcVβ12 unique, primer hcVβ72 unique, primer hcVβ21 unique, primer dtb54 unique or primer dtb182 unique, in combination with Cβ3 primer (SEQ ID NO:59). PCR reactions were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30 sec., about 72°C for about 1 min. for about 35 cycles; then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM $MgCl_2$, about 1 unit Amplitaq Gold, about 0.1 μM dNTP's and about 0.4 μM primer. PCR products were resolved by electrophoresis on an about 1.2% LE agarose gel in TBE buffer and stained with ethidium bromide.

The results shown in Fig. 1A indicated that PCR products using cells isolated from the control dog were generated using all 7 Vβ specific primers. In addition, the levels of PCR products were substantially the same using the 7 Vβ specific primers. The results shown in Fig. 1B and 1C indicated that the Vβ profiles of PCR products using cells isolated from the lymphoma dog Haynes, or the lymphoma dog Stoll, were different from the Vβ profile of the control dog. In particular, T cells expressing hcVβ21 genes have been expanded in both patients, while T cells expressing the other 6 Vβ genes have decreased in proportion.

Taken together, the results disclosed in Examples 3 and 4 indicate that primers complementary to unique Vβ sequences of the present invention can be used to: (1) detect the presence of specific Vβ genes in a population of cells; (2) identify clonal expansion of cells expressing a particular Vβ gene; and (3) associate clonal T cell

expansion with an abnormal state or disease; or (4) distinguish a general lymphoproliferative state involving polyclonal T cell activation from clonal T cell expansion.

Example 6

This example describes a method for DNA fingerprinting the junctional regions of rearranged Vβ genes to identify clonal expansion of T cells.

DNA sequence analysis of the junction between the V, D and J regions of a Vβ gene can determine whether a mRNA population that translates into a Vβ protein is homogenous or heterogeneous by looking at the fluorescent DNA fingerprint. Fluorescent DNA fingerprints of Vβ mRNA populations were determined as follows. cDNA was prepared using standard methods from mitogen stimulated canine PBL cells isolated from a control dog and from lymph node cells isolated from the lymphoma dog Haynes or. The cDNA samples from either Haynes or the control dog were used as templates for PCR reactions using variable region primers in combination with constant region primers. Use of such primers were designed so that the resulting PCR products span the D/J junction of a Vβ cDNA. Primer hcVβ3 unique, primer hcVβ4 unique, primer hcVβ12 unique, primer hcVβ72 unique, primer hcVβ21 unique, primer dtb54 unique or primer dtb182 unique, was used in combination with the Cβ3 primer (SEQ ID NO:59). PCR reactions were performed using the following conditions: Taq activation was performed at about 95°C for about 10 min., about 94°C for about 30 sec., about 60°C for about 30 sec., about 72°C for about 1 min. for about 35 cycles; then clonal extension was performed at about 72°C for about 5 min.; PCR was performed in a reaction buffer containing 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.01% gelatin, pH 3, 3 mM $MgCl_2$, about 1 unit Amplitaq Gold, about 0.1 μM dNTP's and about 0.4 μM primer.

About 20-25 μl of each resulting PCR product was resolved by electrophoresis on an about 1.2% LE agarose gel in TBE buffer and stained with ethidium bromide. DNA bands of about 400 bp identified on the gel were excised and the DNA purified. The purified DNA was sequenced using the Cβ2 primer (SEQ ID NO:58) using standard fluorescent dyes and an automated DNA sequencer.

Fluorescent electrophoretic histograms were generated for sequence obtained using each primer and each template. Fig. 2 illustrates 7 histograms generated using cDNA from the control dog and each of the 4 Vβ primers. The histograms show the typical heterogeneity of a T cell population in a normal dog. These histograms indicate that the DNA sequences of a particular amplified Vβ PCR product can be determined through the first about 120 bp of the Vβ constant region, but become ambiguous as the sequence profile enters the heterogenous J/D junctional regions.

Fig. 3 illustrates 4 histograms generated using cDNA from the lymphoma dog Haynes and Vβ primers hcVβ12 unique, hcVβ72 unique, hcVβ21 unique, dtb54 unique or dtb182 unique. The histograms show that 3 of the 4 Vβ genes amplified have fingerprints similar to those seen with a heterogeneous population of T cells, such as shown in Fig. 2. The histogram generated using the hcvb21 unique primer has a fingerprint which allows the unambiguous determination of the DNA sequence throughout the entire junctional region between the V, D, J and C regions. This result indicates that the sequence recognized by the hcvb21 unique primer was dominant among the canine PBL cell population from the lymphoma dog.

A comparison of the histogram generated using the hcvb21 unique primer with cDNA from the normal dog with the histogram generated using the hcvb21 unique primer with cDNA from the lymphoma dog is shown in Fig. 4. The comparison illustrates that the difference between the two histograms can be used to determine clonal expansion of a single T cell and association of such expansion to an abnormal state or disease.

Example 7

This example describes the generation of T cell clones reactive to flea saliva allergens, and the characterization of the TCR Vβ genes used by the T cell receptors of the T cell clones.

It is to be noted that this example includes a number of cellular immunology techniques considered to be familiar to those skilled in the art. Disclosure of such techniques can be found, for example, in Coligan et al., *Current Protocol in Immunology,* Wiley Interscience, New York. T cell clones reactive to flea saliva

antigens were generated from peripheral blood mononuclear cells (PBMC) isolated from the experimentally-induced flea allergic dog CPO2 (described in U.S. Patent No. 5,646,115, issued on July 8, 1997) as follows. Blood samples were isolated from experimentally-induced flea allergic dog CPO2. Peripheral blood lymphocytes (PBL) were harvested from each sample by centrifugation using a ficoll gradient (available from Pharmacia). The PBL cells were cultured in about 5 ml cultures in culture medium containing IMDM and 10% fetal calf serum (available from Gibco, Gaithersburg, MD) at about 5 X 10^6 cells/ml in the presence of about 5 μg/ml flea saliva protein (prepared according to the methods described in U.S. Patent No. 5,646,115) for about 14 days, at about 37°C, in about 5% CO_2. The incubated cells were harvested and the number of viable cells determined. The viable cells were plated in 96 well round bottom plates at about 10^2 or about 10^3 cells per well per 200 μl of culture medium in the presence of about 10^5 autologous irradiated PBL (prepared according to the methods generally described in Coligan, *ibid.*) as antigen presenting cells (APC), about 5 μg/ml of flea saliva protein, and about 10 units/ml of recombinant hIL-2 for another 14 days. Wells that contain growing cells were restimulated *in situ* by replacing about 150 μl of spent culture medium (i.e., medium in which cells had been grown) with about 150 μl of fresh culture medium, flea saliva protein and APC as described above. About 10-14 days later, cultures in which the T cells were actively proliferating were transferred into 48 well plates, and tested for antigen specificity by comparing growth of the cells in the presence of flea saliva protein and APC, with growth of cells in the presence of APC alone. Cells that required flea saliva protein and APC to grow were selected and expanded in the presence of APC and flea saliva protein. These expanded cells are referred to as T cell clones.

Seven different T cell clones were derived from cells isolated from CPO2. mRNA was prepared from about 10^6 cells from each of the 7 clones using standard methods. cDNA was prepared from the mRNA using methods described above in Example 1. The cDNA samples from the 7 clones were then used as templates in PCR reactions to determine the presence of particular TCR Vβ molecules using the methods described above in Example 4. Analysis of the resulting PCR products indicated that 6

of the 7 clones expressed TCR using the dtb182 V beta chain, thereby indicating a bias in TCR Vβ usage in the T cell reactivity of CPO2 to flea saliva protein.

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such modifications and adaptations are within the scope of the present invention, as set forth in the following claims.

What is claimed is:

1. An isolated protein comprising a protein selected from the group consisting of:

(a) an isolated protein having an amino acid sequence that is at least about 55 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:29, SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 amino acids in length;

(b) an isolated protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:32, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 15 amino acids in length;

(c) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:10, SEQ ID NO:35, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 25 amino acids in length; and

(d) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:15, SEQ ID NO:38, SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 35 amino acids in length.

2. An isolated protein comprising a protein selected from the group consisting of:

(a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

(b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of

SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment that is at least about 30 nucleotides in length;

(c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and

(d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

3. An isolated nucleic acid molecule having a nucleic acid sequence that is selected from the group consisting of:

(a) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, SEQ ID NO:30 and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

(b) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, SEQ ID NO:33, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of

SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length;

(c) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, SEQ ID NO:36, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, and the complement of a nucleic acid sequence that encodes an amino acid sequence selecte from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:67, or a fragment thereof that is at least about 40 nucleotides in length;

(d) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, SEQ ID NO:39, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, and the complement of a nucleic acid sequence that encodes an amino acid sequence selecte from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length; and

(e) a nucleic acid sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

4. An isolated nucleic acid molecule selected from the group consisting of:

(a) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30, or a fragment thereof, wherein said fragment has an at least a 20 contiguous nucleotide region identical in sequence to a 20 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, and SEQ ID NO:30;

(b) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, and SEQ ID NO:33, or a fragment thereof,

wherein said fragment has an at least a 25 contiguous nucleotide region identical in sequence to a 25 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31 and SEQ ID NO:33;

(c) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36, or a fragment thereof, wherein said fragment has an at least a 30 contiguous nucleotide region identical in sequence to a 30 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:36; and

(d) an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39, or a fragment thereof, wherein said fragment has an at least a 60 contiguous nucleotide region identical in sequence to a 60 contiguous nucleotide region of a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, and SEQ ID NO:39.

5. An isolated nucleic acid molecule having a nucleic acid sequence encoding a protein selected from the group consisting of:

(a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

(b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of

SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length;

(c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and

(d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

6. An isolated oligonucleotide comprising a unique nucleic acid sequence within a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID

NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, and SEQ ID NO:80; and a homolog thereof.

7. A reagent that is unique to a nucleic acid molecule selected from the group consisting of $nCaV\beta3_{381}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta3_{333}$, $nCaV\beta4_{351}$, $nCaV\beta12_{339}$, $nCaV\beta72_{423}$, $nCaV\beta21_{396}$, $nCaV\beta54_{354}$ and $nCaV\beta182_{369}$, wherein said reagent can distinguish one member of said group from another member of said group.

8. A method to detect expansion of T cells in an animal comprising:

(a) identifying the presence of one or more T cell receptor nucleic acid molecule(s) having unique nucleic acid sequences within variable regions of beta chain nucleic acid molecules selected from the group consisting of $nCaV\beta3_{381}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta3_{333}$, $nCaV\beta4_{351}$, $nCaV\beta12_{339}$, $nCaV\beta72_{423}$, $nCaV\beta21_{396}$, $nCaV\beta54_{354}$ and $nCaV\beta182_{369}$ by forming detectable products; and

(b) detecting the expansion of said T cells by determining production of said product.

9. A therapeutic composition that, when administered to an animal, regulates an immune response in said animal, said therapeutic composition comprising a therapeutic compound selected from the group consisting of:

(i) an isolated protein comprising a TCR Vβ protein selected from the group consisting of:

(a) an isolated protein having an amino acid sequence that is at least about 55 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:29, SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 amino acids in length;

(b) an isolated protein having an amino acid sequence that is at least about 75 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:32, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 15 amino acids in length;

(c) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group

consisting of SEQ ID NO:10, SEQ ID NO:35, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 25 amino acids in length; and

(d) an isolated protein having an amino acid sequence that is at least about 50% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:15, SEQ ID NO:38, SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 35 amino acids in length;

(ii) a mimetope of any of said TCR Vβ proteins;

(iii) a chimeric form of any of said TCR Vβ proteins;

(iv) an isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:28, SEQ ID NO:30 and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

(b) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:31, SEQ ID NO:33, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, and the complement of a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment thereof that is at least about 30 nucleotides in length;

(c) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:34, SEQ ID NO:36, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, and the complement

of a nucleic acid sequence that encodes an amino acid sequence selecte from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:67, or a fragment thereof that is at least about 40 nucleotides in length;

(d) a nucleic acid sequence that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:37, SEQ ID NO:39, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, and the complement of a nucleic acid sequence that encodes an amino acid sequence selecte from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length; and

(e) a nucleic acid sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56;

(v) an isolated antibody that selectively binds to any of said TCR Vβ proteins; and

(vi) an inhibitor of TCR Vβ protein activity identified by its ability to inhibit the activity of said TCR Vβ proteins.

10. A method to produce a TCR Vβ protein, said method comprising culturing a cell capable of expressing said protein, said protein selected from the group consisting of:

(a) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:28, SEQ ID NO:50, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, or a fragment thereof that is at least about 25 nucleotides in length;

(b) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:31, SEQ ID NO:51, and a nucleic acid

sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, or a fragment that is at least about 30 nucleotides in length;

(c) a protein encoded by a nucleic acid molecule that is at least about 70 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:34, SEQ ID NO:52, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, or a fragment thereof that is at least about 40 nucleotides in length; and

(d) a protein encoded by a nucleic acid molecule that is at least about 75 percent identical to a nucleic acid sequence selected from the group consisting of SEQ ID NO:98, SEQ ID NO:17, SEQ ID NO:37, SEQ ID NO:53, and a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, or a fragment thereof that is at least about 75 nucleotides in length.

11. The invention of Claim 1, 2, 9 or 10, wherein said protein, when administered to an animal, can perform a function selected from the group consisting of eliciting an immune response against a TCR Vβ protein and binding to a MHC molecule that binds to a TCR Vβ protein.

12. The invention of Claim 1, 2, 9 or 10, wherein said protein is selected from the group consisting of: a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 and SEQ ID NO:71; and a protein encoded by an allelic variant of a nucleic acid molecule encoding a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 and SEQ ID NO:71.

13. An isolated antibody that selectively binds to a protein as set forth in the invention of Claim 1, 2, 9 or 10.

14. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule comprises a nucleic acid sequence that encodes a TCR Vβ protein.

15. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule encodes a protein that elicits an immune response against a naturally-occurring TCR Vβ protein.

16. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule comprises a nucleic acid molecule selected from the group consisting of $nCaV\beta3_{381}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta3_{333}$, $nCaV\beta4_{351}$, $nCaV\beta12_{339}$ and $nCaV\beta72_{423}$.

17. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule is selected from the group consisting of: a nucleic acid molecule comprising a nucleic acid sequence that encodes a protein having an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:5, SEQ ID NO:10, SEQ ID NO:15, SEQ ID NO:29, SEQ ID NO:32, SEQ ID NO:35, SEQ ID NO:38, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70 and SEQ ID NO:71; and a nucleic acid molecule comprising an allelic variant of a nucleic acid molecule encoding a protein having any of said amino acid sequences.

18. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule is selected from the group consisting of: a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17 and SEQ ID NO:18; and a nucleic acid molecule comprising an allelic variant of a nucleic acid molecule comprising any of said nucleic acid sequences.

19. The nucleic acid molecule of the invention of Claim 3-10, wherein said nucleic acid molecule comprises an oligonucleotide.

20. A recombinant molecule comprising a nucleic acid molecule as set forth in the invention of Claim 3-10 operatively linked to a transcription control sequence.

21. A recombinant virus comprising a nucleic acid molecule as set forth in the invention of Claim 3-10.

22. A recombinant cell comprising a nucleic acid molecule as set forth in the invention of Claim 3-10.

23. The invention of Claim 3-10, wherein said nucleic acid molecule comprises an oligonucleotide from about 15 nucleotides to about 25 nucleotides in length.

24. The invention of Claim 3-10, wherein said nucleic acid molecule comprises an oligonucleotide selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

25. The invention of Claim 3-10, wherein said nucleic acid molecule has a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

26. The invention of Claim 3-10, wherein said invention comprises a reagent which identifies the presence of a T cell receptor having a unique nucleic acid sequence within said nucleic acid molecule.

27. The invention of Claim 3-10, wherein said invention comprises a reagent which is a DNA primer complementary to said unique nucleic acid sequence.

28. The invention of Claim 3-10, wherein said invention comprises a unique nucleic acid sequence that is selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and SEQ ID NO:56.

29. A kit comprising said reagent of Claim 7, wherein said kit comprises one or more of said reagents and a means for detecting said reagents.

30. A kit comprising said reagent of Claim 7, wherein said kit comprises seven of said reagents, wherein each of said seven reagents identifies the presence of a different beta chain V region selected from the group consisting of $nCaV\beta3_{381}$, $nCaV\beta4_{408}$, $nCaV\beta4_{384}$, $nCaV\beta12_{408}$, $nCaV\beta12_{402}$, $nCaV\beta72_{438}$, $nCaV\beta72_{399}$, $nCaV\beta3_{333}$, $nCaV\beta4_{351}$, $nCaV\beta12_{339}$, $nCaV\beta72_{423}$, $nCaV\beta21_{396}$, $nCaV\beta54_{354}$ and $nCaV\beta182_{369}$.

31. The kit of Claim 30, wherein said kit further comprises a DNA primer complementary to a nucleic acid sequence in the constant region of a T cell receptor beta chain.

32. The kit of Claim 30, wherein said constant region nucleic acid sequence is selected from the group consisting of SEQ ID NO:58 and SEQ ID NO:59.

33. The kit of Claim 30, wherein said kit comprises a composition comprising a mixture of said reagents and said DNA primer complementary to a nucleic acid sequence in the constant region of a T cell receptor beta chain.

34. The method of Claim 8, wherein said step of detecting comprises comparing formation of one detectable product with one or more other detectable products.

35. The method of Claim 8, wherein said variable region has a nucleic acid sequence selected from the group consisting of SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, and complements of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56.

36. The method of Claim 8, wherein said step of identification comprises:

(a) contacting a sample containing DNA from T cells with a reagent having specificity for one of said unique nucleic acid sequences; and

(b) determining the presence of DNA carrying said unique nucleic acid sequence.

37. The method of Claim 8, wherein said reagent is a DNA primer that is complementary to said unique nucleic acid sequence.

38. The method of Claim 8, wherein said step of identification is performed using polymerase chain reaction amplification.

39. The method of Claim 8, wherein said method detects a disease that is selected from the group consisting of cancer, an autoimmune disease, an infectious disease and allergy.

40. The invention of Claim 8 or 9, wherein said animal is selected from the group consisting of an animal suspected of having a disease, an animal having a disease and an animal being treated for a disease, wherein said disease is selected from the group consisting of lymphoma, leukemia, rheumatoid arthritis, diabetes, viral infections, bacterial infections, yeast infections, parasite infections, dermatitis, and asthma.

41. The method of Claim 40, wherein said disease is selected from the group consisting of T cell lymphoma and T cell leukemia.

42. A composition comprising the invention of Claim 1, 2, 3, 4, 5, 6, or 9, wherein said composition further comprises a component selected from the group consisting of an excipient, an adjuvant and a carrier.

43. The composition of Claim 9, wherein said therapeutic compound is selected from the group consisting of a peptide, a naked nucleic acid vaccine and a recombinant cell vaccine.

44. A method to regulate an immune response in an animal comprising administering to the animal a therapeutic composition comprising the invention of Claim 1, 2, 3, 4, 5, 6, or 9.

45. A method for prescribing treatment for specific disease, comprising:

(a) identifying the presence of a T cell receptor nucleic acid molecule having a unique nucleic acid sequence within a variable region of a beta chain nucleic

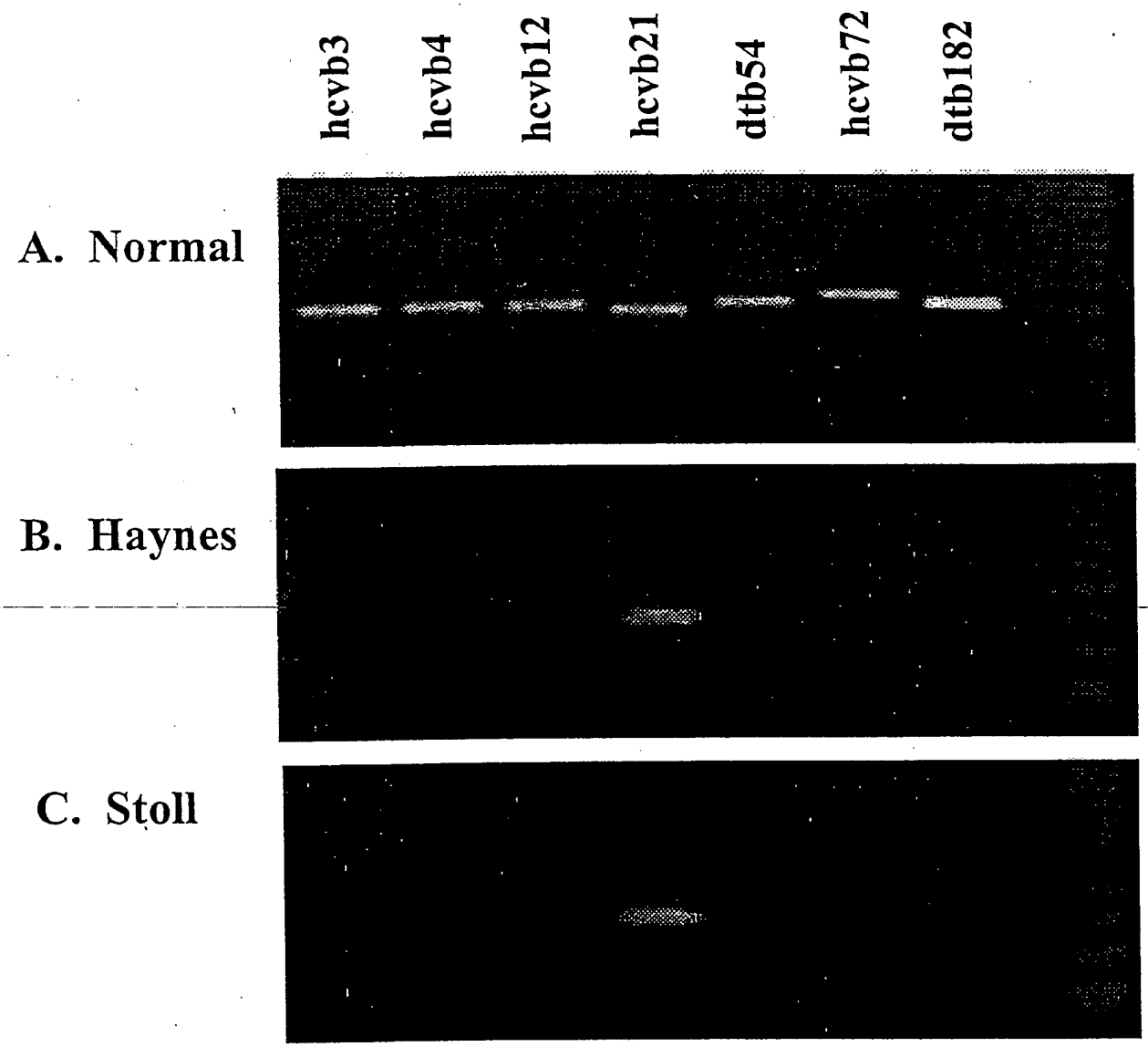
acid molecule selected from the group consisting of $nCaV\beta3_{333}$, $nCaV\beta4_{351}$, $nCaV\beta12_{339}$, $nCaV\beta72_{423}$, $nCaV\beta21_{396}$, $nCaV\beta54_{354}$, $nCaV\beta182_{369}$, $nCaV\beta3_{381}$, $nCaV\beta4_{408}$, $nCaV\beta12_{408}$, $nCaV\beta72_{438}$, $nCaV\beta21_{462}$, $nCaV\beta54_{417}$ and $nCaV\beta182_{423}$; and

(b) prescribing a treatment comprising administering to said animal a therapeutic composition comprising the invention of Claim 1, 2, 3, 4, 5, 6, or 9.

46. The reagent of Claim 7, wherein said reagent identifies the presence of a T cell receptor having a unique nucleic acid sequence within said nucleic acid molecule.

47. The reagent of Claim 7, wherein said reagent is a DNA primer complementary to said unique nucleic acid sequence.

48. The reagent of Claim 7, wherein said unique nucleic acid sequence is selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55 and SEQ ID NO:56.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hcvb4
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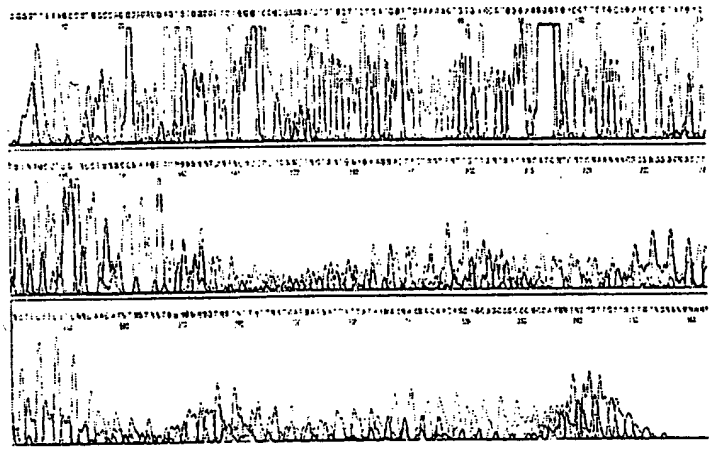
A. Normal
B. Haynes
C. Stoll

Fig. 1

hcvb3



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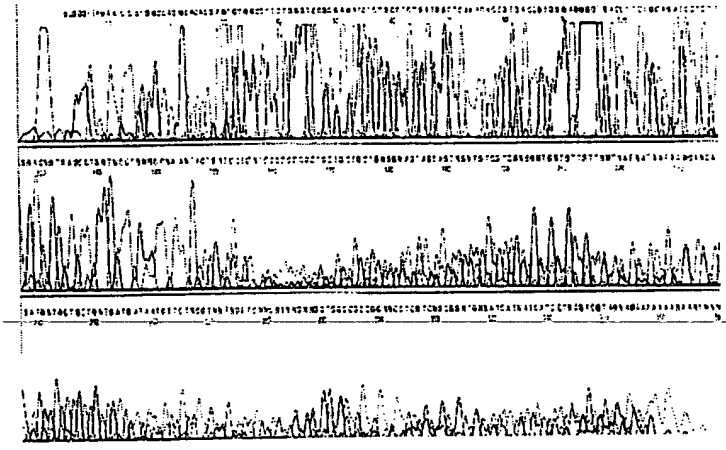

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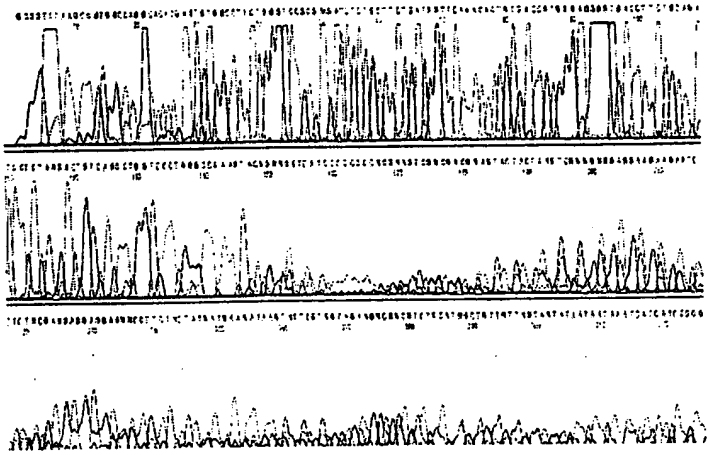

Fig. 2A

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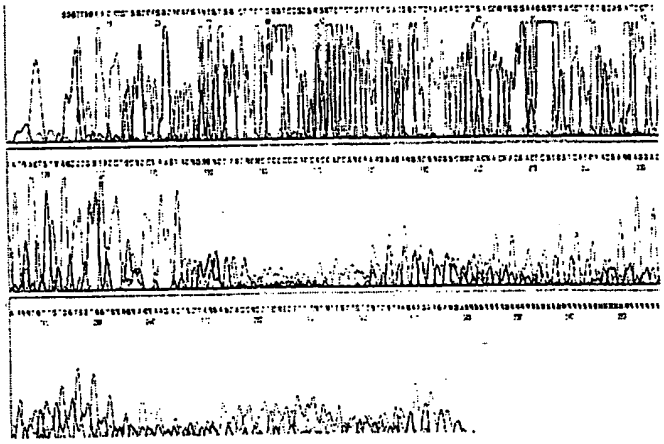

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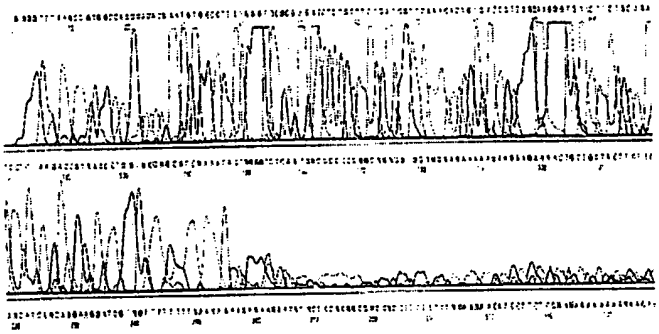

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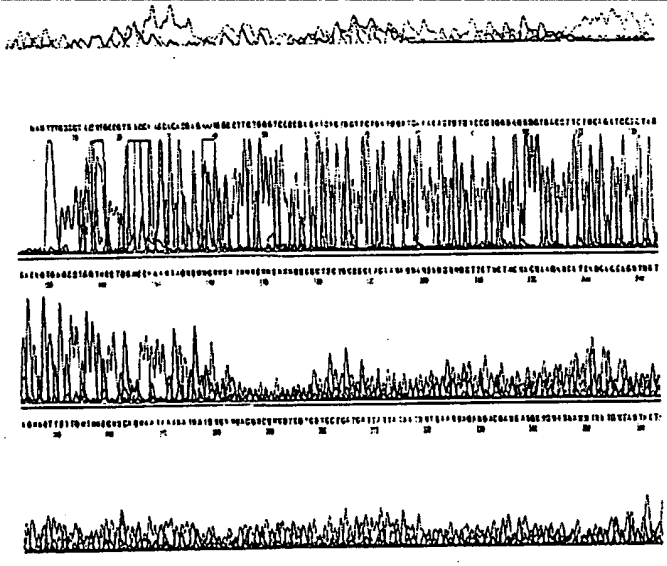

Fig. 2B

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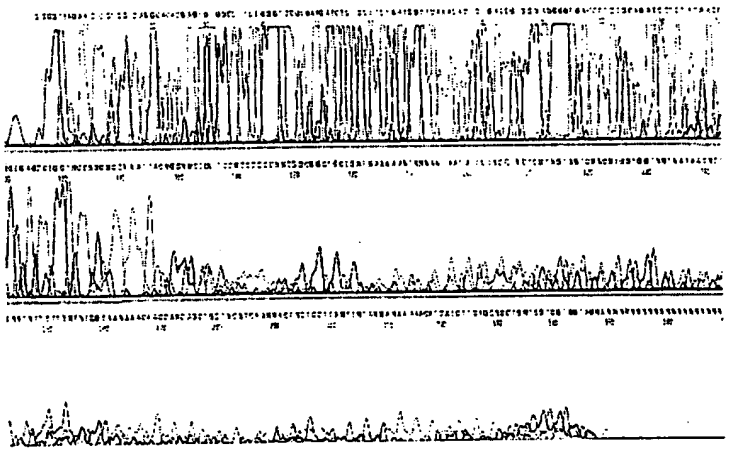

Fig. 2C

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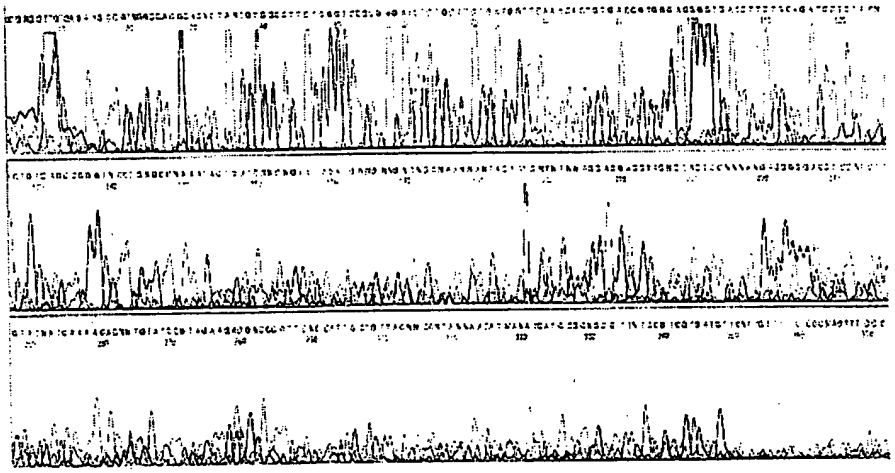

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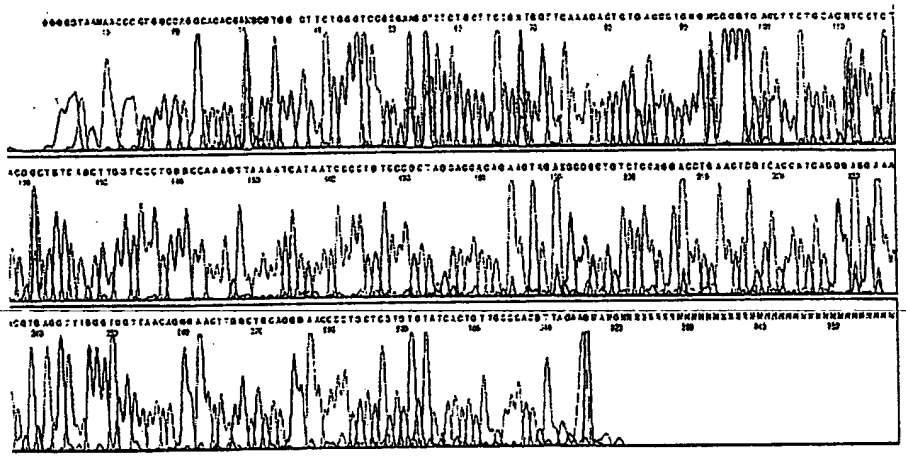

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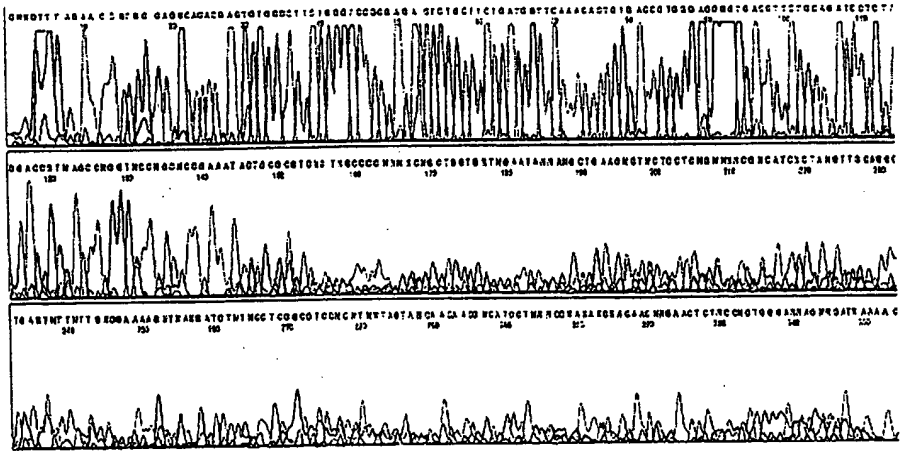

Fig. 3A

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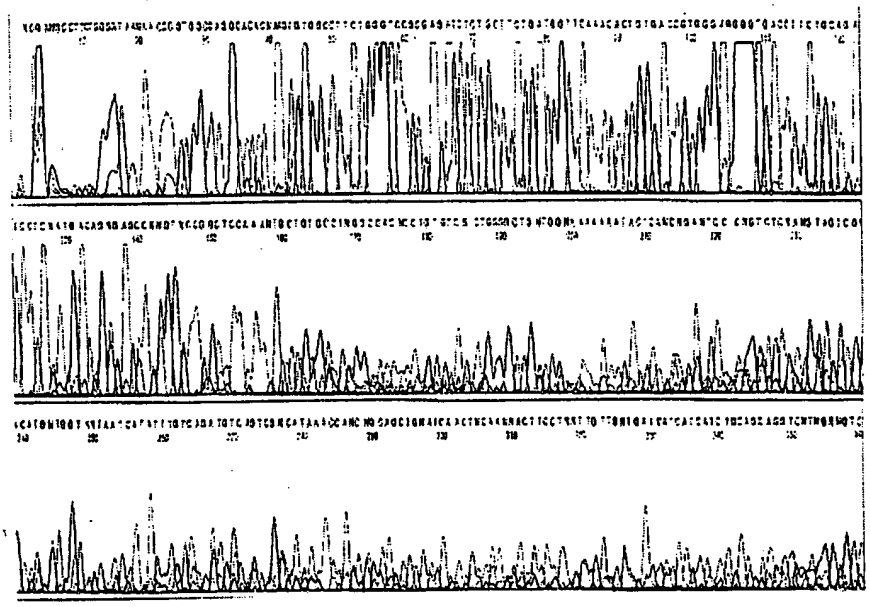

Fig. 3B

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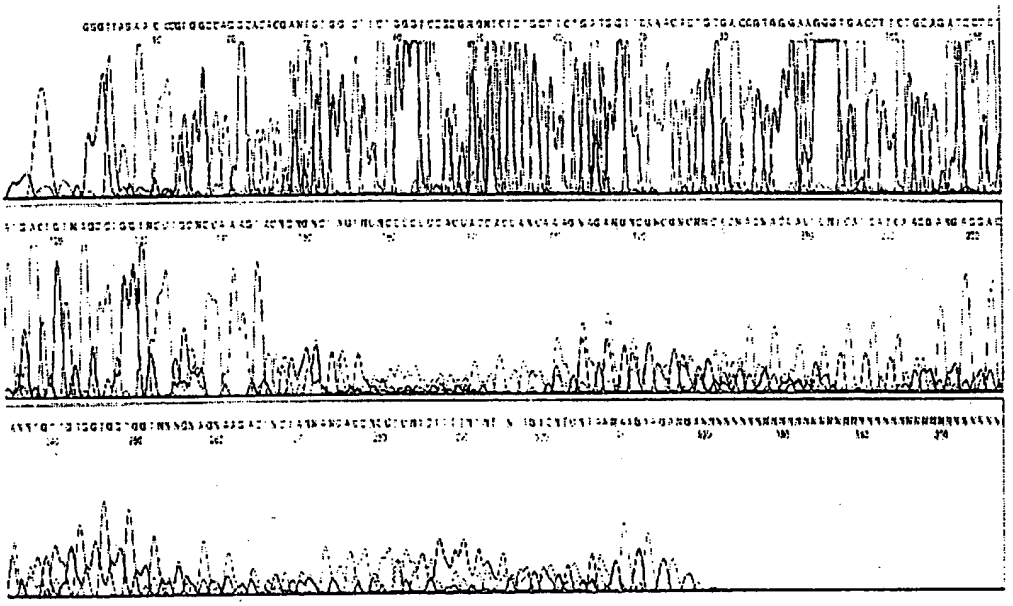

Haynes hcvb21

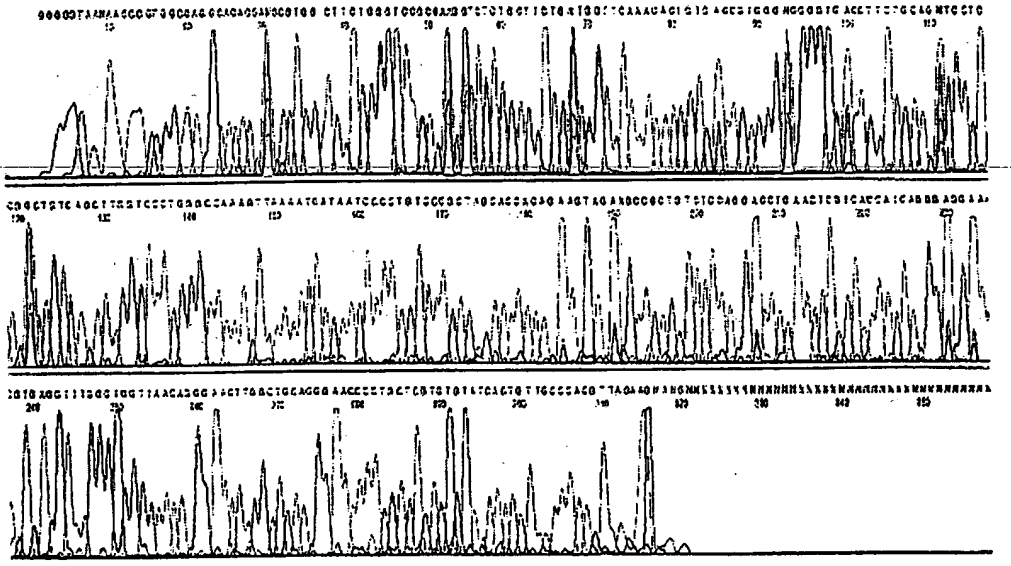

Fig. 4

SEQUENCE LISTING

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Dreitz, Matthew J.

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agtgctgtta ataccatttg aataatagat cagcctcggc ccatgtccca ggtcatgtcg 240

ataccagtac atatagtcat agttgtctgt ctggtgacat ctcagagtca ccctctttcc 300

tgtccctgtg accttgtatc ttgggctctg gataattcca gcatccatgt atcctgtcca 360

caggacacaa agagccatgc caaagaagac gccggtggcc at 402

<210> 14
<211> 483
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (85)..(483)

<400> 14
aattaaccct cactaaaggg aacaaaagct ggagctccac cgcggcacga ggagcgggga 60

```
ggctatcagc ttcccagggc tgcc atg ggc tcc agg ctt ctc tgc tgt gtg    111
                          Met Gly Ser Arg Leu Leu Cys Cys Val
                            1               5
```

```
gcc ctt tgt ctc ctg gga gcc ggc ccc gtg gag tct gag gtc atc caa   159
Ala Leu Cys Leu Leu Gly Ala Gly Pro Val Glu Ser Glu Val Ile Gln
 10                  15                  20                  25

act cca aga cac atg atc aaa gca aga gga cag aca gtg acc ctg aga   207
Thr Pro Arg His Met Ile Lys Ala Arg Gly Gln Thr Val Thr Leu Arg
                 30                  35                  40

tgt tcc ctt atc tct gga cac cta tct gtg tac tgg tac caa cag gcc   255
Cys Ser Leu Ile Ser Gly His Leu Ser Val Tyr Trp Tyr Gln Gln Ala
             45                  50                  55

ctg ggc cag ggt ccc cgg ttt ctc att cag tat tac aat agg gaa gag   303
Leu Gly Gln Gly Pro Arg Phe Leu Ile Gln Tyr Tyr Asn Arg Glu Glu
         60                  65                  70

aga gac aaa gga gac atc ccg gca aga ttc tca gtg cag cag ttc agt   351
Arg Asp Lys Gly Asp Ile Pro Ala Arg Phe Ser Val Gln Gln Phe Ser
     75                  80                  85

aac tac agc tcc cag ctg gag atg aac tcc ctg gag cca gga gac tca   399
Asn Tyr Ser Ser Gln Leu Glu Met Asn Ser Leu Glu Pro Gly Asp Ser
 90                  95                 100                 105

gcc cta tat ctc tgt gcc agc agc tta gat gcg ttc gac gcg ggg cag   447
Ala Leu Tyr Leu Cys Ala Ser Ser Leu Asp Ala Phe Asp Ala Gly Gln
                110                 115                 120

ctg tac ttc ggg gcc ggt tcc aag ctg gcc gtg ctg                   483
Leu Tyr Phe Gly Ala Gly Ser Lys Leu Ala Val Leu
            125                 130
```

<210> 15
<211> 133
<212> PRT
<213> Canis familiaris

<400> 15

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Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
  1               5                  10                  15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
             20                  25                  30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
         35                  40                  45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
```

50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
100 105 110

Ser Leu Asp Ala Phe Asp Ala Gly Gln Leu Tyr Phe Gly Ala Gly Ser
115 120 125

Lys Leu Ala Val Leu
130

<210> 16
<211> 483
<212> DNA
<213> Canis familiaris

<400> 16
cagcacggcc agcttggaac cggccccgaa gtacagctgc cccgcgtcga acgcatctaa 60

gctgctggca cagagatata gggctgagtc tcctggctcc agggagttca tctccagctg 120

ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 180

ctcttcccta ttgtaatact gaatgagaaa ccggggaccc tggcccaggg cctgttggta 240

ccagtacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 300

tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 360

gagacaaagg gccacacagc agagaagcct ggagcccatg gcagccctgg gaagctgata 420

gcctccccgc tcctcgtgcc gcggtggagc tccagctttt gttcccttta gtgagggtta 480

att 483

<210> 17
<211> 399
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(399)

<400> 17
atg ggc tcc agg ctt ctc tgc tgt gtg gcc ctt tgt ctc ctg gga gcc 48
Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

ggc ccc gtg gag tct gag gtc atc caa act cca aga cac atg atc aaa 96
Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
20 25 30

gca aga gga cag aca gtg acc ctg aga tgt tcc ctt atc tct gga cac 144
Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
35 40 45

cta tct gtg tac tgg tac caa cag gcc ctg ggc cag ggt ccc cgg ttt 192
Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
50 55 60

ctc att cag tat tac aat agg gaa gag aga gac aaa gga gac atc ccg 240
Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

gca aga ttc tca gtg cag cag ttc agt aac tac agc tcc cag ctg gag 288
Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
85 90 95

atg aac tcc ctg gag cca gga gac tca gcc cta tat ctc tgt gcc agc 336
Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
100 105 110

agc tta gat gcg ttc gac gcg ggg cag ctg tac ttc ggg gcc ggt tcc 384
Ser Leu Asp Ala Phe Asp Ala Gly Gln Leu Tyr Phe Gly Ala Gly Ser
115 120 125

---

aag ctg gcc gtg ctg 399
Lys Leu Ala Val Leu
130

<210> 18
<211> 399
<212> DNA
<213> Canis familiaris

<400> 18
cagcacggcc agcttggaac cggccccgaa gtacagctgc cccgcgtcga acgcatctaa 60

gctgctggca cagagatata gggctgagtc tcctggctcc agggagttca tctccagctg 120
ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 180

ctcttcccta ttgtaatact gaatgagaaa ccggggaccc tggcccaggg cctgttggta 240

ccagtacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 300

tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 360

gagacaaagg gccacacagc agagaagcct ggagcccat 399

<210> 19
<211> 462
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (73)..(462)

<400> 19
gctgcaggat tcggcacgag gcgtggtcat atctatcttg agagaggtat ggtatgaggc 60

catcacctga ag atg ctg atg ctt ctg ctg ctc ctg ggg ccc agc tct gga 111
Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly
1 5 10

ctc ggt gcc ctc gtc ttc cag gcg ccc agc aca atg atc tgt aag agc 159
Leu Gly Ala Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser
15 20 25

gga gcc acc gtg cag atc cag tgt caa aca gtg gac ctt caa gcc aca 207
Gly Ala Thr Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr
30 35 40 45

acc gtg ttt tgg tat cgc cag ctc ccg aag cag ggc ctt acc ctt atg 255
Thr Val Phe Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met
50 55 60

gtg acc tct aac gtg ggc aac agt gct aca cac gag cag ggg ttc cct 303
Val Thr Ser Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro
65 70 75

gca gcc aag ttc cct gtt aac cac cca aac ctc acg ttt tcc tcc ctg 351
Ala Ala Lys Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu
80 85 90

atg gtg acg agt tca ggt cct gga gac agc ggc ctc tac ttc tgt ggt 399
Met Val Thr Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Gly
95 100 105

gtt cgg gcg tat ggt ggg aac tcg ccc ctc tac ttt gga aca ggc acc 447
Val Arg Ala Tyr Gly Gly Asn Ser Pro Leu Tyr Phe Gly Thr Gly Thr
110 115 120 125

agg ctc acc gtg aca
Arg Leu Thr Val Thr
130

462

<210> 20
<211> 130
<212> PRT
<213> Canis familiaris

<400> 20
Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
1 5 10 15

Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
20 25 30

Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
50 55 60

Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
65 70 75 80

Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
85 90 95

Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Gly Val Arg Ala
100 105 110

Tyr Gly Gly Asn Ser Pro Leu Tyr Phe Gly Thr Gly Thr Arg Leu Thr
115 120 125

Val Thr
130

<210> 21
<211> 462
<212> DNA
<213> Canis familiaris

<400> 21
tgtcacggtg agcctggtgc ctgttccaaa gtagaggggc gagttcccac catacgcccg 60

aacaccacag aagtagaggc cgctgtctcc aggacctgaa ctcgtcacca tcagggagga 120

```
aaacgtgagg tttgggtggt taacagggaa cttggctgca gggaacccct gctcgtgtgt 180

agcactgttg cccacgttag aggtcaccat aagggtaagg ccctgcttcg ggagctggcg 240

ataccaaaac acggttgtgg cttgaaggtc cactgtttga cactggatct gcacggtggc 300

tccgctctta cagatcattg tgctgggcgc ctggaagacg agggcaccga gtccagagct 360

gggccccagg agcagcagaa gcatcagcat cttcaggtga tggcctcata ccatacctct 420

ctcaagatag atatgaccac gcctcgtgcc gaatcctgca gc                    462


<210> 22
<211> 417
<212> DNA
<213> Canis familiaris
<220>
<221> CDS
<222> (13)..(417)

<400> 22
cacgagcctg cc atg tgc cca gtg ttc atc tgc tcc ttg gtc ctc tgg ctc 51
              Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu
                1               5                  10

ctg agt aca ggc acc ctc aat gca aaa gtc atg cag act cca gga cat   99
Leu Ser Thr Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His
     15                  20                  25

ctg gtc aaa ggg aaa gga caa aaa gca aaa atg gaa tgt gtc cca ata   147
Leu Val Lys Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile
 30                  35                  40                  45

aaa gga cat agt tat gtt ttc tgg tat cag cag atc cca gca aaa gag   195
Lys Gly His Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu
                 50                  55                  60

ttc aag ttc ttg att tct ttc cag gat aac gct gtc ttt gat aaa aca   243
Phe Lys Phe Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr
             65                  70                  75

ggg atg ccc acg cag aga ttt tta gcc ttg tgt cca aaa aac cta ccc   291
Gly Met Pro Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro
         80                  85                  90

tgt agc cta gag atc gag cgt aca gag ctg cag gat tca gcc gtg tat   339
Cys Ser Leu Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr
     95                  100                 105

ttt tgt gcc agc agt gac aga act ggg gga ctc gtt cac gag cag tat   387
```

```
Phe Cys Ala Ser Ser Asp Arg Thr Gly Gly Leu Val His Glu Gln Tyr
110                 115                 120                 125

ttc ggc gcc ggc acc agg ctc acg gtc ctc                         417
Phe Gly Ala Gly Thr Arg Leu Thr Val Leu
                130                 135
```

<210> 23
<211> 135
<212> PRT
<213> Canis familiaris

<400> 23

```
Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
 1               5                  10                  15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
            20                  25                  30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
        35                  40                  45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
    50                  55                  60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
65                  70                  75                  80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
                85                  90                  95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Ala
            100                 105                 110

Ser Ser Asp Arg Thr Gly Gly Leu Val His Glu Gln Tyr Phe Gly Ala
        115                 120                 125

Gly Thr Arg Leu Thr Val Leu
    130                 135
```

<210> 24
<211> 417
<212> DNA
<213> Canis familiaris

<400> 24

```
gaggaccgtg agcctggtgc cggcgccgaa atactgctcg tgaacgagtc ccccagttct 60
```

gtcactgctg gcacaaaaat acacggctga atcctgcagc tctgtacgct cgatctctag 120

gctacagggt aggtttttg gacacaaggc taaaaatctc tgcgtgggca tccctgtttt 180

atcaaagaca gcgttatcct ggaaagaaat caagaacttg aactcttttg ctgggatctg 240

ctgataccag aaaacataac tatgtccttt tattgggaca cattccattt ttgctttttg 300

tcctttccct ttgaccagat gtcctggagt ctgcatgact tttgcattga gggtgcctgt 360

actcaggagc cagaggacca aggagcagat gaacactggg cacatggcag gctcgtg 417

<210> 25
<211> 423
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (40)..(423)

<400> 25
ggcacgagca ctgaggacca gactgtgcct gtctccacc atg ggc tcc ggg ttc 54
Met Gly Ser Gly Phe
1 5

ctc tgc tgt atg gtc ctc tgc ctc ctg gga gca gca ccc ctg gac aca 102
Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala Ala Pro Leu Asp Thr
10 15 20

aca gtt tcc cag act cca aga tac ctc atc gcg cac gtg gga tcg aag 150
Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala His Val Gly Ser Lys
25 30 35

aag tta cta aaa tgt gag caa aat ctg ggc cat aat gct atg tac tgg 198
Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His Asn Ala Met Tyr Trp
40 45 50

tat aag caa gac ctc aag caa ctg ctg aag atc atg ttt atc tac ttt 246
Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile Met Phe Ile Tyr Phe
55 60 65

aat cag gga ctc aat cta aat gaa tca gtt cca ggt cgt ttc tca cct 294
Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro Gly Arg Phe Ser Pro
70 75 80 85

gag aca ctg aca agc tca tta act tca tgt cga ctc ctg aac agt gac 342
Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg Leu Leu Asn Ser Asp
90 95 100

```
tct gct gtg tat ttc tgt gcc agc agc gag ggg tat gat gaa aaa ttg   390
Ser Ala Val Tyr Phe Cys Ala Ser Ser Glu Gly Tyr Asp Glu Lys Leu
            105                 110                 115

tat ttt gca agt gga acc aag ctt tct gtc ttg                      423
Tyr Phe Ala Ser Gly Thr Lys Leu Ser Val Leu
        120                 125
```

<210> 26
<211> 128
<212> PRT
<213> Canis familiaris

<400> 26

```
Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
  1               5                  10                  15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
             20                  25                  30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
         35                  40                  45

Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
     50                  55                  60

Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
 65                  70                  75                  80

Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
                 85                  90                  95

Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Ala Ser Ser Glu Gly
            100                 105                 110

Tyr Asp Glu Lys Leu Tyr Phe Ala Ser Gly Thr Lys Leu Ser Val Leu
        115                 120                 125
```

<210> 27
<211> 423
<212> DNA
<213> Canis familiaris

<400> 27

```
caagacagaa agcttggttc cacttgcaaa atacaatttt tcatcatacc cctcgctgct 60

ggcacagaaa tacacagcag agtcactgtt caggagtcga catgaagtta atgagcttgt 120

cagtgtctca ggtgagaaac gacctggaac tgattcattt agattgagtc cctgattaaa 180
```

gtagataaac atgatcttca gcagttgctt gaggtcttgc ttataccagt acatagcatt 240

atggcccaga ttttgctcac attttagtaa cttcttcgat cccacgtgcg cgatgaggta 300

tcttggagtc tgggaaactg ttgtgtccag gggtgctgct cccaggaggc agaggaccat 360

acagcagagg aacccggagc ccatggtgga gacaggcaca gtctggtcct cagtgctcgt 420

gcc 423

<210> 28
<211> 333
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(333)

<400> 28

```
atc gga ctc ctc tgt ggt gtg gcc ttt tgt ttc ctg gga gta ggc ctt   48
Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
  1               5                  10                  15

ttg aac gca caa gtg act caa acc ccg aga caa ctc atc aaa aaa gtg   96
Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
             20                  25                  30

gga gcg aaa gtt ttg ttg aaa tgt tca cag aat atg gac cat gaa aga   144
Gly Ala Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
         35                  40                  45
```

```
atg ttc tgg tat cga caa gac cca ggt ctg ggg ttg cgg ctg ctc tac   192
Met Phe Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
     50                  55                  60

tgg tcc tat aat att gac agt gtt gag aca gga gac atc cct tat ggg   240
Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
 65                  70                  75                  80

tac agt gtc tcg agg aag aag aag gat gcc ttc ccc ttg att ctg gag   288
Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
                 85                  90                  95

tct gct cgc atc aac cag aca tct gtg tac ttc tgc gcc agc agc       333
Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Ala Ser Ser
            100                 105                 110
```

<210> 29
<211> 111
<212> PRT
<213> Canis familiaris
<400> 29

```
Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
  1               5                  10                  15

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
             20                  25                  30

Gly Ala Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
         35                  40                  45

Met Phe Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
     50                  55                  60

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
 65                  70                  75                  80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
                 85                  90                  95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Ala Ser Ser
            100                 105                 110
```

<210> 30
<211> 333
<212> DNA
<213> Canis familiaris

<400> 30

```
gctactggcg cagaagtaca cagatgtctg gttgatgcga gcagactcca gaatcaaggg 60

gaaggcatcc ttcttcttcc tcgagacact gtacccataa gggatgtctc ctgtctcaac 120

actgtcaata ttataggacc agtagagcag ccgcaacccc agacctgggt cttgtcgata 180

ccagaacatt ctttcatggt ccatattctg tgaacatttc aacaaaactt tcgctcccac 240

ttttttgatg agttgtctcg gggtttgagt cacttgtgcg ttcaaaaggc ctactcccag 300

gaaacaaaag gccacaccac agaggagtcc gat                              333
```

<210> 31
<211> 351
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (25)..(351)

<400> 31
acggtgaagg gctagcacct aaag atg ctg act tgc ctg cta ctc ctc ctg 51
Met Leu Thr Cys Leu Leu Leu Leu Leu
1 5

gga caa ggc tct gtg ttt gga gct ctt gtc tct caa aag ccg cgc agg 99
Gly Gln Gly Ser Val Phe Gly Ala Leu Val Ser Gln Lys Pro Arg Arg
10 15 20 25

gac atc tgt caa cgt ggg acc tcc att acc atc cac tgt gag gtc gat 147
Asp Ile Cys Gln Arg Gly Thr Ser Ile Thr Ile His Cys Glu Val Asp
30 35 40

acc caa gtc acc ttg atg ttc tgg tac cgt cag ctc cca gga cag agc 195
Thr Gln Val Thr Leu Met Phe Trp Tyr Arg Gln Leu Pro Gly Gln Ser
45 50 55

ttg ata ctg att gca acc gca aac cag ggt gca gag gcc acc tac gaa 243
Leu Ile Leu Ile Ala Thr Ala Asn Gln Gly Ala Glu Ala Thr Tyr Glu
60 65 70

agt gga ttt acc agg gag aag ttt ccc atc agc cgc cga acc cta atg 291
Ser Gly Phe Thr Arg Glu Lys Phe Pro Ile Ser Arg Arg Thr Leu Met
75 80 85

ttc tcc act ctg act gtg agc aac ctg agc ctc gaa gac acc agc tct 339
Phe Ser Thr Leu Thr Val Ser Asn Leu Ser Leu Glu Asp Thr Ser Ser
90 95 100 105

tac ttc tgc agc 351
Tyr Phe Cys Ser

<210> 32
<211> 109
<212> PRT
<213> Canis familiaris

<400> 32
Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
1 5 10 15

Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe

```
        35                  40                  45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
     50                  55                  60

Asn Gln Gly Ala Glu Ala Thr Tyr Glu Ser Gly Phe Thr Arg Glu Lys
 65                  70                  75                  80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
                 85                  90                  95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Ser
            100                 105
```

<210> 33
<211> 351
<212> DNA
<213> Canis familiaris

<400> 33
gctgcagaag taagagctgg tgtcttcgag gctcaggttg ctcacagtca gagtggagaa 60

cattagggtt cggcggctga tgggaaactt ctccctggta aatccacttt cgtaggtggc 120
ctctgcaccc tggtttgcgg ttgcaatcag tatcaagctc tgtcctggga gctgacggta 180

ccagaacatc aaggtgactt gggtatcgac ctcacagtgg atggtaatgg aggtcccacg 240

ttgacagatg tccctgcgcg gcttttgaga gacaagagct ccaaacacag agccttgtcc 300

caggaggagt agcaggcaag tcagcatctt taggtgctag cccttcaccg t 351

<210> 34
<211> 339
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (7)..(339)

<400> 34
```
gctgaa atg gcc acc ggc gtc ttc ttt ggc atg gct ctt tgt gtc ctg    48
       Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu
         1               5                  10

tgg aca gga tac atg gat gct gga att atc cag agc cca aga tac aag   96
Trp Thr Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys
 15                  20                  25                  30
```

```
gtc aca ggg aca gga aag agg gtg act ctg aga tgt cac cag aca gac   144
Val Thr Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp
                35                  40                  45

aac tat gac tat atg tac tgg tat cga cat gac ctg gga cat ggg ccg   192
Asn Tyr Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro
            50                  55                  60

agg ctg atc tat tat tca aat ggt att aac agc act gaa aaa gga gac   240
Arg Leu Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp
        65                  70                  75

ctc tcc aat gga tac aca gtc tct aga tca aac aag atg gat ttc ccc   288
Leu Ser Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro
    80                  85                  90

ctc cta ctg gac tct gtt acc tcc tcc cag aca tct gtg tac ttc tgt   336
Leu Leu Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys
95                  100                 105                 110

gcc                                                              339
Ala
```

<210> 35
<211> 111
<212> PRT
<213> Canis familiaris

<400> 35
Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
1   5   10   15

Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
            20   25   30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
        35   40   45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
    50   55   60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
65   70   75   80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
                85   90   95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Ala
            100   105   110

<210> 36
<211> 339
<212> DNA
<213> Canis familiaris

<400> 36
ggcacagaag tacacagatg tctgggagga ggtaacagag tccagtagga gggggaaatc 60

catcttgttt gatctagaga ctgtgtatcc attggagagg tctccttttt cagtgctgtt 120

aataccattt gaataataga tcagcctcgg cccatgtccc aggtcatgtc gataccagta 180

catatagtca tagttgtctg tctggtgaca tctcagagtc accctctttc ctgtccctgt 240

gaccttgtat cttgggctct ggataattcc agcatccatg tatcctgtcc acaggacaca 300

aagagccatg ccaaagaaga cgccggtggc catttcagc 339

<210> 37
<211> 423
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (85)..(423)

<400> 37
aattaaccct cactaaaggg aacaaaagct ggagctccac cgcggcacga ggagcgggga 60

ggctatcagc ttcccagggc tgcc atg ggc tcc agg ctt ctc tgc tgt gtg 111
Met Gly Ser Arg Leu Leu Cys Cys Val
1 5

gcc ctt tgt ctc ctg gga gcc ggc ccc gtg gag tct gag gtc atc caa 159
Ala Leu Cys Leu Leu Gly Ala Gly Pro Val Glu Ser Glu Val Ile Gln
10 15 20 25

act cca aga cac atg atc aaa gca aga gga cag aca gtg acc ctg aga 207
Thr Pro Arg His Met Ile Lys Ala Arg Gly Gln Thr Val Thr Leu Arg
30 35 40

tgt tcc ctt atc tct gga cac cta tct gtg tac tgg tac caa cag gcc 255
Cys Ser Leu Ile Ser Gly His Leu Ser Val Tyr Trp Tyr Gln Gln Ala
45 50 55

ctg ggc cag ggt ccc cgg ttt ctc att cag tat tac aat agg gaa gag 303
Leu Gly Gln Gly Pro Arg Phe Leu Ile Gln Tyr Tyr Asn Arg Glu Glu
60 65 70

aga gac aaa gga gac atc ccg gca aga ttc tca gtg cag cag ttc agt 351
Arg Asp Lys Gly Asp Ile Pro Ala Arg Phe Ser Val Gln Gln Phe Ser
75 80 85

aac tac agc tcc cag ctg gag atg aac tcc ctg gag cca gga gac tca 399
Asn Tyr Ser Ser Gln Leu Glu Met Asn Ser Leu Glu Pro Gly Asp Ser
90 95 100 105

gcc cta tat ctc tgt gcc agc agc 423
Ala Leu Tyr Leu Cys Ala Ser Ser
110

<210> 38
<211> 113
<212> PRT
<213> Canis familiaris

<400> 38
Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
100 105 110

Ser

<210> 39
<211> 423
<212> DNA
<213> Canis familiaris

<400> 39
gctgctggca cagagatata gggctgagtc tcctggctcc agggagttca tctccagctg 60

ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 120

ctcttcccta ttgtaatact gaatgagaaa ccggggaccc tggcccaggg cctgttggta 180

ccagtacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 240

tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 300

gagacaaagg gccacacagc agagaagcct ggagcccatg gcagccctgg gaagctgata 360

gcctccccgc tcctcgtgcc gcggtggagc tccagctttt gttcccttta gtgagggtta 420

att 423

<210> 40
<211> 396
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (73)..(396)

<400> 40
gctgcaggat tcggcacgag gcgtggtcat atctatcttg agagaggtat ggtatgaggc 60

catcacctga ag atg ctg atg ctt ctg ctg ctc ctg ggg ccc agc tct gga 111
Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly
1 5 10

ctc ggt gcc ctc gtc ttc cag gcg ccc agc aca atg atc tgt aag agc 159
Leu Gly Ala Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser
15 20 25

gga gcc acc gtg cag atc cag tgt caa aca gtg gac ctt caa gcc aca 207
Gly Ala Thr Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr
30 35 40 45

acc gtg ttt tgg tat cgc cag ctc ccg aag cag ggc ctt acc ctt atg 255
Thr Val Phe Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met
50 55 60

gtg acc tct aac gtg ggc aac agt gct aca cac gag cag ggg ttc cct 303
Val Thr Ser Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro
65 70 75

gca gcc aag ttc cct gtt aac cac cca aac ctc acg ttt tcc tcc ctg 351
Ala Ala Lys Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu
80 85 90

atg gtg acg agt tca ggt cct gga gac agc ggc ctc tac ttc tgt 396
Met Val Thr Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys
95 100 105

<210> 41
<211> 108
<212> PRT
<213> Canis familiaris

<400> 41
Met Leu Met Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
1 5 10 15

Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
20 25 30

Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
50 55 60

Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
65 70 75 80

Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
85 90 95

Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys
100 105

<210> 42
<211> 396
<212> DNA
<213> Canis familiaris

<400> 42
acagaagtag aggccgctgt ctccaggacc tgaactcgtc accatcaggg aggaaaacgt 60

gaggtttggg tggttaacag ggaacttggc tgcagggaac ccctgctcgt gtgtagcact 120

gttgcccacg ttagaggtca ccataagggt aaggccctgc ttcgggagct ggcgatacca 180

aaacacggtt gtggcttgaa ggtccactgt ttgacactgg atctgcacgg tggctccgct 240

cttacagatc attgtgctgg gcgcctggaa gacgagggca ccgagtccag agctgggccc 300

caggagcagc agaagcatca gcatcttcag gtgatggcct cataccatac ctctctcaag 360

atagatatga ccacgcctcg tgccgaatcc tgcagc 396

<210> 43
<211> 354
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (13)..(354)

<400> 43
cacgagcctg cc atg tgc cca gtg ttc atc tgc tcc ttg gtc ctc tgg ctc 51
Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu
1 5 10

ctg agt aca ggc acc ctc aat gca aaa gtc atg cag act cca gga cat 99
Leu Ser Thr Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His
15 20 25
ctg gtc aaa ggg aaa gga caa aaa gca aaa atg gaa tgt gtc cca ata 147
Leu Val Lys Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile
30 35 40 45

aaa gga cat agt tat gtt ttc tgg tat cag cag atc cca gca aaa gag 195
Lys Gly His Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu
50 55 60

ttc aag ttc ttg att tct ttc cag gat aac gct gtc ttt gat aaa aca 243
Phe Lys Phe Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr
65 70 75

ggg atg ccc acg cag aga ttt tta gcc ttg tgt cca aaa aac cta ccc 291
Gly Met Pro Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro
80 85 90

tgt agc cta gag atc gag cgt aca gag ctg cag gat tca gcc gtg tat 339
Cys Ser Leu Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr
95 100 105

ttt tgt gcc agc agt 354
Phe Cys Ala Ser Ser
110

<210> 44
<211> 114
<212> PRT
<213> Canis familiaris

<400> 44
Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Ala
100 105 110

Ser Ser

<210> 45
<211> 354
<212> DNA
<213> Canis familiaris

<400> 45
actgctggca caaaaataca cggctgaatc ctgcagctct gtacgctcga tctctaggct 60

acagggtagg ttttttggac acaaggctaa aaatctctgc gtgggcatcc ctgttttatc 120

aaagacagcg ttatcctgga aagaaatcaa gaacttgaac tcttttgctg ggatctgctg 180

ataccagaaa acataactat gtccttttat tgggacacat tccatttttg ctttttgtcc 240

tttccctttg accagatgtc ctggagtctg catgactttt gcattgaggg tgcctgtact 300

caggagccag aggaccaagg agcagatgaa cactgggcac atggcaggct cgtg 354

<210> 46
<211> 369
<212> DNA
<213> Canis familiaris

<220>

<221> CDS
<222> (40)..(369)

<400> 46
ggcacgagca ctgaggacca gactgtgcct gtctccacc atg ggc tcc ggg ttc 54
Met Gly Ser Gly Phe
1 5

ctc tgc tgt atg gtc ctc tgc ctc ctg gga gca gca ccc ctg gac aca 102
Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala Ala Pro Leu Asp Thr
10 15 20

aca gtt tcc cag act cca aga tac ctc atc gcg cac gtg gga tcg aag 150
Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala His Val Gly Ser Lys
25 30 35

aag tta cta aaa tgt gag caa aat ctg ggc cat aat gct atg tac tgg 198
Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His Asn Ala Met Tyr Trp
40 45 50

tat aag caa gac ctc aag caa ctg ctg aag atc atg ttt atc tac ttt 246
Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile Met Phe Ile Tyr Phe
55 60 65

aat cag gga ctc aat cta aat gaa tca gtt cca ggt cgt ttc tca cct 294
Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro Gly Arg Phe Ser Pro
70 75 80 85

gag aca ctg aca agc tca tta act tca tgt cga ctc ctg aac agt gac 342
Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg Leu Leu Asn Ser Asp
90 95 100

tct gct gtg tat ttc tgt gcc agc agc 369
Ser Ala Val Tyr Phe Cys Ala Ser Ser
105 110

<210> 47
<211> 110
<212> PRT
<213> Canis familiaris
<400> 47
Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
1 5 10 15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
20 25 30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
35 40 45

Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
50 55 60

Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
65 70 75 80

Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
85 90 95

Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Ala Ser Ser
100 105 110

<210> 48
<211> 369
<212> DNA
<213> Canis familiaris

<400> 48
gctgctggca cagaaataca cagcagagtc actgttcagg agtcgacatg aagttaatga 60

gcttgtcagt gtctcaggtg agaaacgacc tggaactgat tcatttagat tgagtccctg 120

attaaagtag ataaacatga tcttcagcag ttgcttgagg tcttgcttat accagtacat 180

agcattatgg cccagatttt gctcacattt tagtaacttc ttcgatccca cgtgcgcgat 240

gaggtatctt ggagtctggg aaactgttgt gtccaggggt gctgctccca ggaggcagag 300

gaccatacag cagaggaacc cggagcccat ggtggagaca ggcacagtct ggtcctcagt 360

gctcgtgcc 369

<210> 49
<211> 504
<212> DNA
<213> Canis familiaris

<400> 49
gaggatctgc agaaggtcac ccctcccacg gtcacagtgt ttgaaccatc ggaagcagag 60

atctcgcgga cccagaaggc cacactcgtg tgcctggcca cgggcttcta ccccgaccac 120

gtggagctga gctggtgggt gaacgggaag gaggtcacga gtgggttcag caccgacccg 180

cagccctaca aggagaggcc cagcgagaat gactccagct actgtctgag cagccggctg 240

agggtctctg cctccttctg gcacaacccg cgcaaccact tccgctgcca agtccagttc 300

tatgggctcg gggacgacga tgagtggaaa tacgatagag tcaaacccat cacccagaac 360

atcagtgctg aggcctgggg cagagcagac tgtggcttca cctcggtgtc ctaccatcag 420

ggcgtcctgt ctgccaccat cctctatgag atcctgctgg gcaaggccac gctgtatgct 480

gtgctggtca gcatcctggt gctg 504

<210> 50
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 50
cgacaagacc caggtctgg 19

<210> 51
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 51
gtcagctccc aggacagag 19

<210> 52
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 52
catgacctgg gacatgggc 19

<210> 53
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 53
gagatgttcc cttatctctg g 21

<210> 54
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 54
cctctaacgt gggcaacag 19

<210> 55
<211> 20
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 55
tcagcagatc ccagcaaaag 20

<210> 56
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 56
agcaagacct caagcaactg 20

<210> 57
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 57
gtgaccttct gcagatcctc 20

<210> 58
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 58
agctcagctc cacgtggtc 19

<210> 59
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 59
tgctgaaccc actcgtgac 19

<210> 60
<211> 109
<212> PRT
<213> Canis familiaris

<220>
<223> At location 109, Xaa = Ala or Ser

<400> 60
Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
1 5 10 15

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
20 25 30

Gly Arg Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
35 40 45

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
50 55 60

Met Phe Trp Tyr Gln Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
65 70 75 80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Xaa
100 105

<210> 61
<211> 110
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 109 and 110, Xaa =Ala or Ser

<400> 61
Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
1 5 10 15

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
20 25 30

Gly Arg Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
35 40 45

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
50 55 60

Met Phe Trp Tyr Gln Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
65 70 75 80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Xaa Xaa
100 105 110

<210> 62
<211> 111
<212> PRT

<213> Canis familiaris

<220>
<223> At locations 109, 110 and 111, Xaa= Ala or Ser

<400> 62
Ile Gly Leu Leu Cys Gly Val Ala Phe Cys Phe Leu Gly Val Gly Leu
1 5 10 15

Leu Asn Ala Gln Val Thr Gln Thr Pro Arg Gln Leu Ile Lys Lys Val
20 25 30

Gly Arg Lys Val Leu Leu Lys Cys Ser Gln Asn Met Asp His Glu Arg
35 40 45

Trp Ser Tyr Asn Ile Asp Ser Val Glu Thr Gly Asp Ile Pro Tyr Gly
50 55 60

Met Phe Trp Tyr Gln Gln Asp Pro Gly Leu Gly Leu Arg Leu Leu Tyr
65 70 75 80

Tyr Ser Val Ser Arg Lys Lys Lys Asp Ala Phe Pro Leu Ile Leu Glu
85 90 95

Ser Ala Arg Ile Asn Gln Thr Ser Val Tyr Phe Cys Xaa Xaa Xaa
100 105 110

<210> 63
<211> 109
<212> PRT
<213> Canis familiaris

<220>
<223> At location 109, Xaa =Ala or Ser

<400> 63
Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
1 5 10 15
Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
50 55 60

Ala Glu Ala Thr Tyr Glu Asn Gln Gly Ser Gly Phe Thr Arg Glu Lys
65 70 75 80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
85 90 95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Xaa
100 105

<210> 64
<211> 110
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 109 and 110, Xaa = Ala or Ser

<400> 64
Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
1 5 10 15

Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
50 55 60

Ala Glu Ala Thr Tyr Glu Asn Gln Gly Ser Gly Phe Thr Arg Glu Lys
65 70 75 80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
85 90 95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Xaa Xaa
100 105 110

<210> 65
<211> 111
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 109, 110 and 111, Xaa =Ala or Ser

<400> 65
Met Leu Thr Cys Leu Leu Leu Leu Leu Gly Gln Gly Ser Val Phe Gly
1 5 10 15
Ala Leu Val Ser Gln Lys Pro Arg Arg Asp Ile Cys Gln Arg Gly Thr
20 25 30

Ser Ile Thr Ile His Cys Glu Val Asp Thr Gln Val Thr Leu Met Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Gly Gln Ser Leu Ile Leu Ile Ala Thr Ala
50 55 60

Ala Glu Ala Thr Tyr Glu Asn Gln Gly Ser Gly Phe Thr Arg Glu Lys
65 70 75 80

Phe Pro Ile Ser Arg Arg Thr Leu Met Phe Ser Thr Leu Thr Val Ser
85 90 95

Asn Leu Ser Leu Glu Asp Thr Ser Ser Tyr Phe Cys Xaa Xaa Xaa
100 105 110

<210> 66
<211> 111
<212> PRT
<213> Canis familiaris

<220>
<223> At location 111, Xaa = Ala or Ser

<400> 66
Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
1 5 10 15

Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
20 25 30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
35 40 45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
50 55 60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
65 70 75 80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
85 90 95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Xaa
100 105 110

<210> 67
<211> 112
<212> PRT

<213> Canis familiaris

<220>
<223> At locations 111 and 112, Xaa = Ala or Ser

<400> 67
Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
1 5 10 15
Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
20 25 30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
35 40 45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
50 55 60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
65 70 75 80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
85 90 95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Xaa Xaa
100 105 110

<210> 68
<211> 113
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 111, 112 and 113, Xaa = Ala or Ser

<400> 68
Met Ala Thr Gly Val Phe Phe Gly Met Ala Leu Cys Val Leu Trp Thr
1 5 10 15

Gly Tyr Met Asp Ala Gly Ile Ile Gln Ser Pro Arg Tyr Lys Val Thr
20 25 30

Gly Thr Gly Lys Arg Val Thr Leu Arg Cys His Gln Thr Asp Asn Tyr
35 40 45

Asp Tyr Met Tyr Trp Tyr Arg His Asp Leu Gly His Gly Pro Arg Leu
50 55 60

Ile Tyr Tyr Ser Asn Gly Ile Asn Ser Thr Glu Lys Gly Asp Leu Ser
65 70 75 80

Asn Gly Tyr Thr Val Ser Arg Ser Asn Lys Met Asp Phe Pro Leu Leu
85 90 95

Leu Asp Ser Val Thr Ser Ser Gln Thr Ser Val Tyr Phe Cys Xaa Xaa
100 105 110

Xaa

<210> 69
<211> 111
<212> PRT
<213> Canis familiaris

<220>
<223> At location 111, Xaa = Ala or Ser

<400> 69
Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Xaa
100 105 110

<210> 70
<211> 112
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 111 and 112, Xaa = Ala or Ser

<400> 70
Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala

1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Xaa Xaa
100 105 110

<210> 71
<211> 113
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 111, 112 and 113, Xaa = Ala or Ser
<400> 71
Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Xaa Xaa
100 105 110

Xaa

<210> 72
<211> 109
<212> PRT
<213> Canis familiaris

<220>
<223> At location 109, Xaa = Ala or Ser

<400> 72
Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
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Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
20 25 30

Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
50 55 60

Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
65 70 75 80

Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
85 90 95

Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Xaa
100 105

<210> 73
<211> 110
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<220>
<223> At location 109 and 110, Xaa = Ala or Ser

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1 5 10 15

Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
20 25 30

Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
50 55 60

Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
65 70 75 80

Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
85 90 95

Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Xaa Xaa
100 105 110

<210> 74
<211> 111
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 109, 110 and 111, Xaa = Ala or Ser

<400> 74
Met Leu Met Leu Leu Leu Leu Leu Gly Pro Ser Ser Gly Leu Gly Ala
1 5 10 15

Leu Val Phe Gln Ala Pro Ser Thr Met Ile Cys Lys Ser Gly Ala Thr
20 25 30

Val Gln Ile Gln Cys Gln Thr Val Asp Leu Gln Ala Thr Thr Val Phe
35 40 45

Trp Tyr Arg Gln Leu Pro Lys Gln Gly Leu Thr Leu Met Val Thr Ser
50 55 60

Asn Val Gly Asn Ser Ala Thr His Glu Gln Gly Phe Pro Ala Ala Lys
65 70 75 80

Phe Pro Val Asn His Pro Asn Leu Thr Phe Ser Ser Leu Met Val Thr
85 90 95

Ser Ser Gly Pro Gly Asp Ser Gly Leu Tyr Phe Cys Xaa Xaa Xaa
100 105 110

<210> 75
<211> 112
<212> PRT
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<220>
<223> At location 112, Xaa = Ala or Ser

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Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Xaa
100 105 110

<210> 76
<211> 113
<212> PRT
<213> Canis familiaris

<220>
<223> At location 112 and 113, Xaa = Ala or Ser

<400> 76
Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Xaa

100 105 110

Xaa

<210> 77
<211> 114
<212> PRT
<213> Canis familiaris

<220>
<223> At location 112, 113 and 114, Xaa = Ala or Ser

<400> 77
Met Cys Pro Val Phe Ile Cys Ser Leu Val Leu Trp Leu Leu Ser Thr
1 5 10 15

Gly Thr Leu Asn Ala Lys Val Met Gln Thr Pro Gly His Leu Val Lys
20 25 30

Gly Lys Gly Gln Lys Ala Lys Met Glu Cys Val Pro Ile Lys Gly His
35 40 45

Ser Tyr Val Phe Trp Tyr Gln Gln Ile Pro Ala Lys Glu Phe Lys Phe
50 55 60

Leu Ile Ser Phe Gln Asp Asn Ala Val Phe Asp Lys Thr Gly Met Pro
65 70 75 80

Thr Gln Arg Phe Leu Ala Leu Cys Pro Lys Asn Leu Pro Cys Ser Leu
85 90 95

Glu Ile Glu Arg Thr Glu Leu Gln Asp Ser Ala Val Tyr Phe Cys Xaa
100 105 110

Xaa Xaa

<210> 78
<211> 108
<212> PRT
<213> Canis familiaris

<220>
<223> At location 108, Xaa = Ala or Ser

<400> 78
Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
1 5 10 15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala

20 25 30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
35 40 45

Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
50 55 60

Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
65 70 75 80

Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
85 90 95

Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Xaa
100 105

<210> 79
<211> 109
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 108 and 109, Xaa = Ala or Ser

<400> 79
Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
1 5 10 15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
20 25 30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
35 40 45

Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
50 55 60

Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
65 70 75 80

Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
85 90 95

Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Xaa Xaa
100 105

<210> 80

<211> 110
<212> PRT
<213> Canis familiaris

<220>
<223> At locations 108, 109 and 110, Xaa = Ala or Ser

<400> 80
Met Gly Ser Gly Phe Leu Cys Cys Met Val Leu Cys Leu Leu Gly Ala
1 5 10 15

Ala Pro Leu Asp Thr Thr Val Ser Gln Thr Pro Arg Tyr Leu Ile Ala
20 25 30

His Val Gly Ser Lys Lys Leu Leu Lys Cys Glu Gln Asn Leu Gly His
35 40 45

Asn Ala Met Tyr Trp Tyr Lys Gln Asp Leu Lys Gln Leu Leu Lys Ile
50 55 60

Met Phe Ile Tyr Phe Asn Gln Gly Leu Asn Leu Asn Glu Ser Val Pro
65 70 75 80

Gly Arg Phe Ser Pro Glu Thr Leu Thr Ser Ser Leu Thr Ser Cys Arg
85 90 95

Leu Leu Asn Ser Asp Ser Ala Val Tyr Phe Cys Xaa Xaa Xaa
100 105 110

<210> 81
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Primer

<220>
<223> Y = T or C , R = G or A, N = A, C, G, or T

<400> 81
ccgaattctg gtaycrnca 19

<210> 82
<211> 18
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<223> Description of Artificial Sequence: Synthetic

Primer

<220>
<223> R = G or A

<400> 82
cggatccgcr cartarta 18

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<220>
<223> R = G or A

<400> 83
cggatccgcr caraarta 18

<210> 84
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<223> Description of Artificial Sequence: Synthetic Primer

<400> 84
ccagacctgg gtcttgtcg 19

<210> 85
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<223> Description of Artificial Sequence: Synthetic Primer

<400> 85
ctctgtcctg ggagctga 18

<210> 86
<211> 21
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<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 86
ttgtttgatc tagagactgt g 21

<210> 87
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<400> 87
atcggactcc tctgtggtgt 20

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acggtgaagg gctagcacct 20

<210> 89
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<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 89
gctgaaatgg ccaccggcgt 20

<210> 90
<211> 19
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 90
ctgttgccca cgttagagg 19

<210> 91
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<400> 92
gctgcaggat tcggcacgag 20

<210> 93
<211> 20
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<220>
<223> Description of Artificial Sequence: Synthetic Primer

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tacgactgtc agcttggtcc 20

<210> 94
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<210> 95
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<212> DNA
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<400> 95
cagttgctta ggtcttgct 19

<210> 96
<211> 20
<212> DNA
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<220>
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<400> 96
cacgagcctg ccatgtgccc 20

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<220>
<223> Description of Artificial Sequence: Synthetic Primer

<400> 97
ggcacgagca ctgaggacca 20

<210> 98
<211> 438
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<220>
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<222> (40)..(438)

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1 5

ctc tgc tgt gtg gcc ctt tgt ctc ctg gga gcc ggc ccc gtg gag tct 102
Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala Gly Pro Val Glu Ser
10 15 20

gag gtc atc caa act cca aga cac atg atc aaa gca aga gga cag aca 150
Glu Val Ile Gln Thr Pro Arg His Met Ile Lys Ala Arg Gly Gln Thr
25 30 35

gtg acc ctg aga tgt tcc ctt atc tct gga cac cta tct gtg tac tgg 198
Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His Leu Ser Val Tyr Trp
40 45 50

tac caa cag gcc ctg ggc cag ggt ccc cgg ttt ctc att cag tat tac 246
Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe Leu Ile Gln Tyr Tyr
55 60 65

aat agg gaa gag aga gac aaa gga gac atc ccg gca aga ttc tca gtg 294
Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro Ala Arg Phe Ser Val
70 75 80 85

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cag cag ttc agt aac tac agc tcc cag ctg gag atg aac tcc ctg gag 342
Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu Met Asn Ser Leu Glu
90 95 100

cca gga gac tca gcc cta tat ctc tgt gcc agc agc tta gat gcg ttc 390
Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Asp Ala Phe
105 110 115

gac gcg ggg cag ctg tac ttc ggg gcc ggt tcc aag ctg gcc gtg ctg 438
Asp Ala Gly Gln Leu Tyr Phe Gly Ala Gly Ser Lys Leu Ala Val Leu
120 125 130

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<212> PRT
<213> Canis familiaris

<400> 99
Met Gly Ser Arg Leu Leu Cys Cys Val Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Gly Pro Val Glu Ser Glu Val Ile Gln Thr Pro Arg His Met Ile Lys
20 25 30

Ala Arg Gly Gln Thr Val Thr Leu Arg Cys Ser Leu Ile Ser Gly His
35 40 45

Leu Ser Val Tyr Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Arg Phe
50 55 60

Leu Ile Gln Tyr Tyr Asn Arg Glu Glu Arg Asp Lys Gly Asp Ile Pro
65 70 75 80

Ala Arg Phe Ser Val Gln Gln Phe Ser Asn Tyr Ser Ser Gln Leu Glu
85 90 95

Met Asn Ser Leu Glu Pro Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
100 105 110

Ser Leu Asp Ala Phe Asp Ala Gly Gln Leu Tyr Phe Gly Ala Gly Ser
115 120 125

Lys Leu Ala Val Leu
130

<210> 100
<211> 438
<212> DNA
<213> Canis familiaris

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cagcacggcc agcttggaac cggccccgaa gtacagctgc cccgcgtcga acgcatctaa 60

gctgctggca cagagatata gggctgagtc tcctggctcc agggagttca tctccagctg 120

ggagctgtag ttactgaact gctgcactga gaatcttgcc gggatgtctc ctttgtctct 180

ctcttcccta ttgtaatact gaatgagaaa ccggggaccc tggcccaggg cctgttggta 240

ccagtacaca gataggtgtc cagagataag ggaacatctc agggtcactg tctgtcctct 300

tgctttgatc atgtgtcttg gagtttggat gacctcagac tccacggggc cggctcccag 360

gagacaaagg gccacacagc agagaagcct ggagcccatg gcagccctgg gaagctgata 420

gcctccccgc tcctcgtg 438

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(51) International Patent Classification 7 :
C12N 15/12, 15/62, 5/10, C07K 14/705, 16/28, C12Q 1/68, A61K 38/17, 31/70, 48/00

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(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/094,506 (CIP)
Filed on 29 July 1998 (29.07.98)

(71) Applicant *(for all designated States except US)*: HESKA CORPORATION [US/US]; 1825 Sharp Point Drive, Fort Collins, CO 80525 (US).

(72) Inventors; and
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(74) Agents: CONNELL, Gary, J. et al.; Sheridan Ross P.C., Suite 3500, 1700 Lincoln Street, Denver, CO 80203-4501 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
4 May 2000 (04.05.00)

(54) Title: T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES, AND USES THEREOF

(57) Abstract

The present invention relates to TCR Vβ proteins; to TCR Vβ nucleic acid molecules, including those that encode such TCR Vβ proteins; to antibodies raised against such TCR Vβ proteins; and to therapeutic compounds that regulate TCR Vβ function. The present invention also includes methods to identify and obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to regulate an immune response in an animal. Also included in the present invention are methods to detect T cell expansion in an animal using reagents including, or derived from such proteins, nucleic acid molecules or antibodies.

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LU	Luxembourg
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MD	Republic of Moldova
MG	Madagascar
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ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
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UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/17309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C12N5/10 C07K14/705 C07K16/28
C12Q1/68 A61K38/17 A61K31/70 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE GENBANK [Online] Accession No. AF082505, 6 January 1999 (1999-01-06) DREITZ M.J. & SIM G.K.: "T cell receptor beta chain hcvb3 (Canis familiaris)" XP002122470 the whole document ---	1-48
X	WO 92 12996 A (IMMUNE RESPONSE CORP INC) 6 August 1992 (1992-08-06) abstract figure 1 examples 1-13 claims 1-113 ---	1-48
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 1999	06. 03. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WEDDERBURN L.R. ET AL.: "In vivo clonal dominance and limited T-cell receptor usage in human CD4+ T-cell recognition of house dust mite allergens" PROC. NATL. ACAD. SCI. USA, vol. 90, September 1993 (1993-09), pages 8214-8218, XP002122467 the whole document -& DATABASE GENBANK [Online] Accession No. Z23040, 17 January 1995 (1995-01-17) WEDDERBURN: "T-cell antigen receptor beta chain" XP002122471 compare seq. IDs 1 and 50 with nt 31-381 and 173-191, respectively ---	1-48
A	TAKANO M. ET AL.: "Identification of dog T-cell receptor beta chain genes" IMMUNOGENETICS, vol. 40, 1994, page 246 XP002122468 cited in the application the whole document ---	1-48
A	ITO K. ET AL.: "Isolation and sequence analysis of cDNA for the dog T-cell receptor Tcr-alpha and Tcr-beta chains" IMMUNOGENETICS, vol. 38, 1993, pages 60-63, XP002122469 cited in the application the whole document ---	1-48
A	US 5 635 354 A (KOURILSKY PHILIPPE ET AL) 3 June 1997 (1997-06-03) abstract -----	1-48

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 99/ 17309

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 44,45
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-48 partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: (1-48) - partially

Isolated nCaV-beta3 polypeptide (seq. IDs 2,29,60,61,62) and homologs.

Corresponding nucleic acids (seq. IDs 1,28) and their allelic variants, complementary DNAs (Seq. ID 3,30), and a unique primer (Seq. ID 50).

Methods to detect expansion of T cells, therapeutic compositions, antibodies,kits.. Uses of said materials in therapeutic, diagnostic and detection applications.

2. Claims: (1-48) - partially

Idem as subject matter 1, but limited to mCaV-beta4 (Seq. IDs 5,32,63,64,65; 4,31,7; 6,33,8; 51)

3. Claims: (1-48) - partially

Idem as subject matter 1, but limited to mCaV-beta12 (Seq. IDs 10,35,66,67,68; 9,34,12; 11,36,13; 52)

4. Claims: (1-48) - partially

Idem as subject matter 1, but limited to mCaV-beta72 (seq. IDs 15,38,69,70,71,99; 37,98,17; 39,100,18; 53)

5. Claims: (3,6-9,20-48) - partially

Idem as subject matter 1, but limited to mCaV-beta21 (seq. IDs 20,72,73,74; 19; 54)

6. Claims: (3,6-9,20-48) - partially

Idem as subject matter 1, but limited to mCaV-beta54 (seq. IDs 23,75,76,77; 22; 24; 55)

7. Claims: (3,6-9,20-48) - partially

Idem as subject matter 1, but limited to mCaV-beta182 (seq. IDs 26,78,79,80; 25; 27; 56).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claim 9 (points i and vi) refer to mimetopes and inhibitors of the polypeptides without giving a true technical characterization. Moreover, no such compounds are defined in the characterization. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

rmation on patent family members

International Application No
PCT/US 99/17309

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